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University of California, Berkeley

History of Science and Technology Program
The Bancroft Library
University of California, Berkeley

Medical Physics Oral History Series

Thomas L. Hayes, Ph.D.
LIPOPROTEIN RESEARCH AND ELECTRON MICROSCOPY AT DONNER LABORATORY

An interview conducted by
Sally Smith Hughes, Ph.D.
in 1980

Since 1954 the Regional Oral History Office has been interviewing leading participants in or well-placed witnesses to major events in the development of northern California, the West, and the nation. Oral history is a method of collecting historical information through tape-recorded interviews between a narrator with firsthand knowledge of historically significant events and a well-informed interviewer, with the goal of preserving substantive additions to the historical record. The tape recording is transcribed, lightly edited for continuity and clarity, and reviewed by the interviewee. The corrected manuscript is indexed, bound with photographs and illustrative materials, and placed in The Bancroft Library at the University of California, Berkeley, and in other research collections for scholarly use. Because it is primary material, oral history is not intended to present the final, verified, or complete narrative of events. It is a spoken account, offered by the interviewee in response to questioning, and as such it is reflective, partisan, deeply involved, and irreplaceable.

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Acknowledgment

This interview with Dr. Thomas Hayes is one of several dealing with the development of the Donner Laboratory and the Division/Department of Medical Physics and Biophysics at the University of California, Berkeley, within the larger series of oral histories produced by the History of Science and Technology Program of The Bancroft Library.

Besides these interviews, the Program assembles other primary source materials, including the papers and personal memorabilia of scientists and engineers, and the papers of certain organizations with which they were associated. The information in the papers and interviews helps to demonstrate the development of science and technology not only in the western United States, but also in the nation as a whole.

The project was made possible initially by the generosity of William R. Hewlett and David Packard. Mrs. Calvin K. Townsend established the Doreen and Calvin K. Townsend Fund to provide ongoing support of the Program. The University Endowment Fund, National Science Foundation, and National Endowment for the Humanities have assisted diverse aspects of the Program with a series of grants. Further aid has come from the Marco Francis Hellman Fund, established to document science and technology and their relations to business in California. The Thomas Hayes oral history was also aided by a gift from the Chabot and Dieckmann Memorial Library Fund. Other donors to the project have included the Woodheath Foundation, the California Alumni Foundation, and the Watkins-Jones Company.

1980
University of California
Berkeley, California

James D. Hart
Director
The Bancroft Library

The Medical Physics Oral History Series

The series, conducted in 1978-1980 under the auspices of the History of Science and Technology Program [HSTP] at The Bancroft Library, was funded by the National Endowment for the Humanities to document medical physics and biophysics at the University of California, Berkeley. Sally Smith Hughes, advised by Roger Hahn and John Heilbron of the Office of the History of Science and Technology, conducted interviews with thirteen individuals associated with Donner and Crocker laboratories and the Division of Medical Physics. All of the interviews had been transcribed and edited when the grant terminated in 1980. Some of the transcripts were subsequently reviewed and approved by the interviewee, processed by various individuals associated with HSTP, and made available for research as bound and indexed volumes. They are: John Gofman, Alexander Grendon, William Myers, Kenneth Scott, and William Siri. Other transcripts have for years remained in various stages of completion, and beginning in 1999, under the aegis of David Farrell, the HSTP curator, are being reconsidered for processing and release. Sally Hughes, of the Regional Oral History Office, has been finalizing the remaining oral histories.

The oral histories, in conjunction with archival holdings at The Bancroft Library and Lawrence Berkeley Laboratory, will be useful in constructing a picture of the growth and development of the fields of medical physics and biophysics, in which the Berkeley research and academic institutions played an early and significant role. The interviews are of particular historical interest for their depiction of the early use of cyclotron-produced radioisotopes and radiations in science and medicine. The series complements other oral histories, at Bancroft Library and at the American Institute of Physics, pertaining to the development of Lawrence Berkeley Laboratory and the subdisciplines of physics.

Sally Smith Hughes, Ph.D.
Research Historian

December 2001
Regional Oral History Office
The Bancroft Library
University of California, Berkeley

HISTORY OF SCIENCE AND TECHNOLOGY PROGRAM
MEDICAL PHYSICS ORAL HISTORIES
March 2002

James L. Born (1915-1981), "Physician and Administrator at Donner Laboratory," 2000

Patricia Durbin-Heavey (b. 1927), "Radionuclide Research at Crocker Laboratory and the Lawrence Berkeley Laboratory," 2002

John Gofman (b. 1918), "John Gofman: Medical Research and Radiation Politics," 1985

Alexander Grendon (1899-1982), "Alexander Grendon: Research with Hardin Jones at Donner Laboratory, 1957-1978," 1985

Thomas L. Hayes (b. 1927), "Lipoprotein Research and Electron Microscopy at Donner Laboratory," 2002

John H. Lawrence (1904-1991), "Nuclear Medicine Pioneer and Director of Donner Laboratory, University of California, Berkeley," 2000

William G. Myers (1908-1988), "William G. Myers: Early History of Nuclear Medicine," 1986

Alexander V. Nichols (b. 1924), "Professor of Biophysics and Lipids Researcher at Berkeley, 1950-1975," 2001

Kenneth G. Scott (1909-1983), "Radioisotope Research in Medicine," 1986

William E. Siri (b. 1919), "William E. Siri: Biophysical Research at Donner Laboratory, 1945-1975," 1987

Cornelius Tobias (1918-2000), unedited manuscript and interview tapes with additional materials deposited in The Bancroft Library, 2001.

IN PROCESS
Howard C. Mel

CURRICULUM VITAE--THOMAS L. HAYES

PERSONAL DATA

Born: 9/12/27, Oakland, California. Father: William Joseph Hayes. Mother: Edith Carew Hayes. Married: 1952, five children. Military Service: U.S. Navy, 1945-1947.

EDUCATION

A.B., Physics, University of California, Berkeley, 1949. Ph.D., Biophysics, University of California, Berkeley, 1955.

MEMBERSHIP, PROFESSIONAL SOCIETIES

Biophysical Society, Electron Microscope Society of America, Royal Microscopical Society, Sigma Xi, Berkeley Chapter, and Northern California Society for Electron Microscopy.

PROFESSIONAL ACTIVITIES

Staff Scientist, 1955-1980, Biology and Medicine Division, Lawrence Berkeley Laboratory.

Staff Senior Scientist, 1980-1991, Deputy Division Head (1980-1986) and Acting Division Head (1982-1983), Biology and Medicine Division, Lawrence Berkeley Laboratory, University of California, Berkeley.

Adjunct Professor of Biophysics, University of California, Berkeley, 1973-1991.

Chairman, Graduate Group in Biophysics, 1977-1979, University of California, Berkeley.

Managing Editor, "Scanning, International Journal of Scanning Electron Microscopy", Witzstrock Publishing, West Germany (with A. Boyde, London and L. Reimer, Munster), 1981-1986.

Editor, 1965-1980, "Advances in Biological and Medical Physics", Academic Press, NY (with J. Lawrence and J. Gofman).

Emeritus Senior Scientist, 1991 to present, Donner Laboratory, Lawrence Berkeley Laboratory, University of California, Berkeley.

CURRICULUM VITAE--THOMAS L. HAYES, page 2.

AWARDS

1. Visiting Fellowship, Clare Hall College, University of Cambridge, England for one year of research on electron microscope techniques. Awarded 1984 for the year September 1986 to September 1987.

2. Senior International Fellowship, U.S. National Institutes of Health, 1987 for research at Cambridge University, England on "Electron Microscopy of Frozen-Hydrated Biospecimens."

3. Lawrence Berkeley Laboratory Program Development Fund Award for research on "Soft X-ray Microscopy in Biological Research". Award made July 27, 1987 for FY 1988.

4. Elected to Life Membership, Clare Hall College, University of Cambridge, Cambridge, England, November 1987.

SELECTED PUBLICATIONS:

T.E. Everhart and T.L. Hayes. "The Scanning Electron Microscope", *Scientific American* 226: 54-69, January, 1972.

T.L. Hayes. In *Advanced Techniques in Biological Electron Microscopy*. J. Koehler, ed., Springer Verlag, New York. "Scanning Electron Microscope Techniques in Biology", pp. 153-214, 1973.

T.L. Hayes. "Trends and Prospects in Scanning Electron Microscopy", *Journal of Microscopy* 100, Pt. 2: 133-143, 1973.

Pawley, J.B., Hook, G., Hayes, T.L. and Lai, C. *Direct Scanning Electron Microscopy of Frozen-Hydrated Yeast*. Scanning 3: 219-226, 1980.

Echlin, P., Lai, C.E., and Hayes, T.L. "Low-temperature X-ray Microanalysis of the Differentiating Vascular Tissue in Root Tips of Lemna minor", *Journal of Microscopy* 126: 285-306, 1982.

INTERVIEW WITH THOMAS HAYES

Family Background and Early Education

[Interview 1: May 6, 1980] ##[1]

Hughes: Dr. Hayes, could you tell me a little bit about your grandparents on both sides?

Hayes: I'm from people that originally lived in Ireland, and so both sides are of Irish background. They came to San Francisco by way of two routes. One side came via Australia and then to San Francisco. Another grandparent's side came by way of the East Coast, Chicago, and across the mainland. All four of my grandparents were here in California fairly early, 1850 or '60. My mother's family, the Carews, lived in San Francisco.

My father's father was superintendent of a mine in a town called Havilah, down not too far from Bakersfield in Kern County. At that time, Havilah was the county seat of Kern County because of the mines. That went along for a while until Bakersfield began to grow up, and they moved the county seat to Bakersfield.

I think the way they got together was when my father [William Joseph Hayes] left the southern part of the state to come to the university here. He was an attorney and judge later on, and went through Boalt Hall here, and met my mother [Edith Carew Hayes], who was coming to Cal from San Francisco.

My mother belonged to a large family. Both families were quite large. She was the first of the girls to go to the university. They generally felt that the girls would go to what was Girl's High then--maybe Girl's High is still there in San Francisco; it was a very good school--and then maybe take another year to become a teacher, but not to go through the full university. But when my mother came along she said, "I'd like to

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[1] ## This symbol indicates that a tape or tape segment has begun or ended. A guide to the tapes follows the transcript.

go to the university," and my grandfather said, "All right," so off she went. She was the only one of her sisters that did that. Several of her brothers went on to college. It wasn't as common for the girls.

So they met here at the university. Then when they were married, they stayed on this side of the bay. They were the Oakland branch; lived for most of the time when I was growing up down by Lake Merritt.

My grandparents had other brothers and sisters that were coming by, so there was a fairly well-established family with cousins. So the group at Havilah--the mines gave out; no more gold, so they moved to Pasadena. And that was where my father's side stayed.

Hughes: Now tell me about your generation. Brothers and sisters?

Hayes: I have a twin brother who is down in the Los Angeles area. I have an older sister and an older brother. My brother is the oldest in the family among the children. We lived in a large house down by Lake Merritt, and I and my brothers and sister went through public schools in that area. I went to Oakland High School, and just about that time it was the beginning of the war.

We were fortunate during the Depression. We clearly could see the Depression all around us, but my father was a referee of bankruptcy--that was his court. It was a bankruptcy court, and of course they were extremely busy. [laughter] Actually, he worked through the Depression as a referee of bankruptcy. So we were fortunate in that the Depression didn't touch us as directly as almost everyone else.

Good times, though, in the sense of the community in that part of the city. Very enjoyable childhood. We tended to do things within the family. My father had died in 1932 when I was five. My mother continued with my older brother, who's about ten years older. He was pretty much the head of the family with my mother during the time that I was growing up.

Hughes: Did she work after your father died?

Hayes: No. She had a teaching credential in French and English. We had some family business and some real estate and some insurance money, and so we got along. [pause] We generally would work hard at school and did well in school. The four of us.

Hughes: Was that important at home?

Hayes: Not much. [laughter] We had very little difficulty in seeing

where the real world was and where the game was. The game was at school, and we liked to play that game. And we generally did pretty well at it.

But I think mostly it comes from the parents. In this case, the mother, because my father had died. She had a healthy disrespect for school even though she went through the university as a fairly early member of women going and she liked school. She thought it was important, but never let it get to the point that it would be a reality in the same sense that the people in the family or even in the neighborhood, friends, and people that you'd meet were.

Hughes: When do you think you began to be interested in the sciences?

Hayes: I think you tend to be interested in things you tend to do well. My older brother was quite a bit older. When he was in high school, he became interested in amateur radio, ham operator. He built his own transmitter and receiver, and used to design and then build them for other people. He came to Cal here in electrical engineering and graduated. I'd have an advantage at school, because almost anything that would come up would've come up at home. He likes to talk. I think we all like to talk in that family. So we'd be talking about things. And so when we came to algebra in school, I already knew what algebra was. It's not so much the day-to-day algebra, but where are you going with algebra? What are the big ideas of algebra? That it deals with the relationship between quantities rather than the quantities themselves.

Hughes: Were these discussions usually just natural occurrences? I mean, he didn't sit down and say, "Well, now, Tom, I'm going to teach you algebra."

Hayes: No, never. I can't even remember that kind of thing. And that applied pretty much all through the family activities. I don't think there was ever a discussion where everybody said, "We're going to talk about being honest." Or, "We're going to talk about being true," or, "We're going to talk about being industrious"--the virtues. Or, "We're going to sit down and talk about avoidance of hurting people." You don't sit down and do that. At least we never did.

We used to like to get a drink of water at night. We'd have to go through his room with all the radio gear and stuff to get this drink of water. We were only six, seven, eight years old, so we'd come trooping through and we could see him operating in there and talking. Then sometimes he'd be sitting there and we'd just talk--he didn't happen to have anybody that he could raise on his ham station. I must say that he had a lot of time going through

high school and college to sit and talk to us, and we had plenty of time to talk to him. And we talked to my mother. If everybody had been so busy learning we never would have learned anything. [laughter]

Not my children. They do hours of this. They're all planned out. And you're supposed to learn this, that, and the other lesson. And they have almost no time left.

Hughes: Well, provided that you have the setting that you had, where something other than the television programming is going in--

Hayes: Well, we used to listen to a lot of radio. There wasn't any television in the thirties, but there was radio. You can't sit down and say you're going to plan to talk about something--you have to have some frames. You interact with people. And one of the frames with us was we were radio-hookers. We had programs that we liked and we'd all sit down and we listened to these programs. Then you start talking about the program. Now, the programs generally were entertaining, but they offered the common experience, something you can then talk about. Pretty soon you'd be talking half the night about something else, but maybe it started with the program. I think if television was there, we'd have watched one of the television shows. Now, I love to watch television still.

We used to go to movies. Movies were a great passion of our family. We used to go to three movies a week. That's a lot of movies. We'd go Wednesday night, Friday night, and Sunday afternoon. That's the whole family, usually. The advantages, I think, are that it provides a community that exists not because you say there should be a community--"By God, we're going to make a community out of this"--because those don't happen, but rather, you have something that people like to do, and so they do it together. Then the community develops.

Hughes: How is your twin fitting into all of this?

Hayes: Oh, I enjoyed being a twin. We had a great time. There was always somebody there. [chuckling] We are not identical twins, and we aren't very much alike in many of the things that we want to do, but sometimes I'd do something that he was starting to get interested in and sometimes he would do something that I would like. There were a lot of arguments, but no serious or lasting disagreements. We used to fight physically when we were little, but those were almost more like play or a sport contest. The arguments are more like a debate. Sometimes you're not even personally involved in the outcome of the debate--it's a position you put forth to see what happens. [laughter] And so we used to

do a lot of that kind of thing, because it's kind of fun to argue. He's a very good arguer.

He's a little different in that he is not so traditional. He went off when we were finished with the navy to do farming on his own down in Arizona--thought he'd start a farm, be self-supporting. In many ways he was kind of like the groups who came later that said, "Be separate, be independent. Grow your own stuff."

Hughes: Is he still doing that?

Hayes: He still does that, yes. I got a card from him around Christmas time. He says, "I've retired." He'd worked many years with the school department. He's a steam fitter and sheet metal worker. He always liked prospecting, so he says, "Now I'm going to prospect, and maybe paint the garage door."

Hughes: And then your sister is the second oldest?

Hayes: She's the second, yes. She's in the middle between the older brother and the twins. My sister is an artist, and her husband is an artist, too--an art historian at the University of Connecticut. She went to Cal here in art.

I always liked art. I taught for a while, part-time, in a fine arts school, at California College of Arts and Crafts.

Hughes: That explains that artistic theme that I see in your papers.

Hayes: Yes.

Hughes: Which came first? Your sister and her interest in art, or was your interest independent?

Hayes: I think mostly it came after the technology. They didn't develop in parallel ways. I think when you're young in technology and in scientific approach, even in the philosophies that tend to be syllogistic where it relies on reasoned approaches, you tend to have more confidence. Then as time goes on, you see that there are not only many, many good answers that you can get from it, but there are many spaces that are left. Or there are many multiple choices equal in reason that have to be faced and one chosen in order to act. So for those choices, you begin to see that the nonrational--not irrational, but maybe arational--approach can be useful. That in many technical people comes a little bit later. That tended to be the way with me. I think in terms of being interested in the technical side of things, in high school I found myself to be pretty well interested in that, whereas the other came more at thirty, something like that.

Whitman College, Berkeley, and the Navy

Undergraduate Education

Hughes: When you went to Whitman, your major was pre-engineering instead of physics. Was that an outgrowth of this technical, radio set background?

Hayes: Yes, I think I would've been in engineering even if I had had a choice. It turned out I didn't have a choice. I went into Whitman College under the navy program, and the navy's students were in engineering.

Hughes: Well, then why the switch very quickly to physics?

Hayes: Well, a couple of things. One is that in talking with the people that I was with during the navy program at Whitman and then some down here--for a while in the navy I lived in the I House [International House, University of California, Berkeley], which was navy during the war. It was kind of like home. We were in school down here as well. So you build up a group of people and they were all pretty much hep people, but they began to look around at the different fields. It seemed at that time that it was very interesting to look at physics.

Physics has a great charm in that it's so nicely neat. It's separated from the engineering thing. You don't have to get the thing to work. What you're dealing with are fundamental kinds of concepts in physics, so it was kind of fun to think about moving into that area. At Whitman College they had a great physics class that I took as part of my engineering. They had a program that made it fun to do the experiments. So when I came down here after the navy you look around for what to do, physics was charming. A very important part of it was the growth in physics and the opportunity in physics--the fact that I was at a school here in Berkeley that had a very excellent physics department.

Hughes: You left Whitman because the war was over. Consequently your obligation with the navy was over?

Hayes: I didn't end it just when I left Whitman because I served, as I say, some down here under that same program. Then I went to flight school; learned to fly under the navy, and then was reassigned, still under the naval air. At that time there wasn't an air force separate from the army and navy, so it was the naval air program.

I went to another naval air station to play basketball. They assigned me as an athletic specialist to play basketball. After I finished my term in the navy, then I did come back to Berkeley to see about a major program.

Hughes: Who were the memorable figures at that stage? Spring '47, you arrived in Berkeley.

Hayes: Yes, I was home from the navy. There were several people that had gone through the navy with me and some people I had known in high school. They were important in that you came back out of the navy to talk with them. Several of them went into physics. I think the most important kinds of discussions, though, were with my older brother. At the beginning of the war he went to the MIT Radiation Lab to work on the beginnings of radar. Then he went to the British branch of the MIT Radiation Lab in England. When he came back, I was still finishing things with the navy, and kind of looking. We used to talk about the different possibilities and it looked like physics was--

Hughes: But he was an engineer.

Hayes: He's an electrical engineer. When he finished his work at MIT, then he went to Seattle and started a company to handle some of the things in radar. What was coming, he said, is television. It's going to make television possible. And it did. Radar made television work.

Hughes: Was he encouraging you to stick with physics?

Hayes: Yes, he thought it looked pretty interesting. We were pretty well encouraged all along. We didn't ever think that there'd be anything else. [laughter] We had problems. I had plenty of courses that were mystery hours, but there was a general feeling, too, at that time, that if you chose your career, the opportunity's there to work through. Really the only thing was which one to choose. Almost everybody that I went to school with ended up professionally in a field of their choice. They also had the opportunity then to continue their education at the graduate level or professional schools. Most every professional school was open to whoever wanted to do it. So that's changed some.

Hughes: Were you going to school under the GI Bill?

Hayes: Yes, when I came back, then I went to school under the GI Bill and the state veterans benefits.

Hughes: Did you have any out of the ordinary relationships with anybody on the faculty as an undergraduate? Any undergraduate research?

Hayes: No, not very much. It's a big school, and physics was a big department. I knew some of the people. I still know some--at least one from physics and he's still here--Alex Nichols.[1] But it's very much, I think, like going to San Francisco to go shopping: you find some nice shops, you like to go to San Francisco, but you really don't expect to meet people. You wouldn't say, "Oh, I'm going over to San Francisco to make friends." You go over to shop. I came to Berkeley to learn physics. I don't know exactly what your "unusual" means, in terms of number of hours of contact or--

Hughes: Well, yes. Sometimes it happens that a student will distinguish himself in some way to such an extent that a faculty member says, "I've got a special project for you." That kind of thing.

Hayes: No, I didn't distinguish myself. [laughter]

Hughes: Well, most of us don't.

Hayes: I remember some great lectures. What I liked in this physics department--people sometimes criticized it and they said, "These people can't teach," but I never have felt that that was any great problem. Some of them couldn't teach very well; I think that was probably true. But they were great physicists, and it was great fun to be in the class and to hear them and to see what they were doing. And if they weren't very well organized, and if they hadn't had time to prepare the lessons, that's a secondary consideration. They knew what physics was about, and that's the most important thing, not where they put the lantern slide on the projector.

Hughes: Did you know at that stage what aspect of physics you were interested in?

Hayes: Well, fairly early. My first two years really were under the engineering program, so I had only two years to go. I came back and took a fairly heavy course load, so I would finish up in those two years. I'd sometimes take eighteen or twenty units a term. So about one year later I had gone to a fair number of physics courses and began to think about what kind of physics I'd like to study. I also thought it was fun to look at biology. I liked biology. I like microscopes. I always liked microscopes. I thought it was always fun to look through a microscope, and so I began to think abut biophysics. So for my senior year I took quite a few biology courses and I talked with the advisor for the fairly new biophysics program. There weren't very many schools that offered biophysics. It looked like it would be fun, so again I talked a lot with my brother. He said it was good.

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[1] See the oral history in this series with Alexander Nichols.

Graduate Student in Biophysics, Berkeley

Hughes: Did you talk to anybody at Donner Laboratory or the Division of Biophysics and Medical Physics?

Hayes: I don't think so.

Hughes: You knew that there was an academic program in biophysics.

Hayes: Yes. I found out about that. I knew who the advisor was and I'd go and say, "If I do get into graduate school, what do I do next? At about that time then I decided that I'd try for graduate school in biophysics.

Hughes: Had graduate school been understood all along?

Hayes: No, not necessarily. My brother never went to graduate school. He has a bachelor in engineering. And I think most engineers in contrast to physicists stop with the bachelor's degree. I think, too, there was a change in the general perception. Graduate school was much more rare before the war than what it was after the war. There was much more assistance, financially, to help you through, and there was a very serious and pervasive dedication to education. When the GIs came back, they generally meant to go through school. And they had great confidence that if they went through school, they would find much better, more satisfying life for the rest of their life.

##

Hayes: The GI Bill was very valuable in helping people be able to go to school. I obviously couldn't have taken the same kind of breadth and course load if I was trying to work at the same time. There was a changeover. Many more people began to think about graduate school, and I was probably one of those.

I didn't really decide on physics until I was a junior. I was for a while in anthropology and archaeology and so on. I took some interesting things in architecture. A lot of my friends were architects. I was thinking maybe I'd be an architect. So I was pretty plastic. I was a junior and still looking. But I had a lot of math and engineering. With that you can move a little more promptly to carry out your decision than if you had to make up this kind of linear progression in mathematics. Mathematics is not so easy to just reach into.

Hughes: Then it was 1950 that you joined the laboratory?

Hayes: Yes, I was in the class of '49 in physics in June. Then I went

into graduate school in the fall of '49. Towards the end of that year or the beginning of 1950, I came to get a job here at Donner with the program that was involved with the lipoproteins. So I came and worked with Jack Gofman, Hardin Jones.

Hughes: How did you know about the position?

Hayes: Alex Nichols and I were taking a night course down at LSB [Life Sciences Building] from Professor Gulberg. Technically just a great course. We were having a lot of fun. It was on optical methods in biology, measuring methods, imaging methods. I think Alex Nichols said he was going to go up to Donner; he'd heard that there were some openings. So I said, "Well, I think I'll try it too." So I came up.

Hughes: This is to support your graduate study?

Hayes: Yes, I was beginning to run out finally of GI support. [laughs] I had worked as an apprentice machinist in the summers in high school but it's nice, of course, if you can combine your field and your work, so I came mostly so that I'd have a chance to see what the work was more than the money. I didn't really come to get a job.

John Gofman and Lipoprotein Research

Hughes: What was the job?

Hayes: The job was reading ultracentrifuge plates. I also began to see a possibility for a graduate program that would involve lipoprotein questions.

Hughes: With Gofman as an advisor?

Hayes: With Gofman as my thesis advisor.

Hughes: Is now the appropriate time to ask you about Gofman and his group?

Hayes: Yes.

Hughes: Well, he seems to be quite a key figure in this whole history. He arrived at Donner Lab just after the war. Did he come with the lipoprotein idea in his back pocket, so to speak?

Hayes: I don't know. I would think probably not that specific, although he may have had some ideas about the lipids and broad ideas about the importance of molecular organization in the serum as a way of

studying disease states. Something like that.

Hughes: Was that an interest that he got in medical school?

Hayes: I think so. I have a kind of recollection of a person who was a very fine chemist over here at Cal, and a very fine medical student over there at UCSF. So it's a real combination. I think he got the Gold Cane in medical school. So he, I think, had some of the approaches from chemistry of the importance of molecular organization that he probably saw was not very strongly represented in the medical school. I think when he went to medical school he saw other qualities and the importance of how you look at disease, whether it's something you tackle, or whether it's something you just kind of accept as part of the broader goal. He was always one of the former.

Hughes: Was that an unusual concept in those days to attempt to link pathology to a molecule?

Hayes: Yes, I think it was. I think it was quite, quite rare to do that. And in some of these diseases that were linked to aging, obviously there were few diseases that were more prevalent than ordinary heart disease. They would sometimes say that they're just part of the physiology, almost. They would assume this. They would accept it as a normal physiological aging process rather than a pathological one. Even if they saw it as pathological, very often I think there was not enough familiarity with molecular structure, with the operation of a physical-chemical system, in order for it to occur to them that there must be something wrong with the molecules.

Hughes: Was it a philosophical barrier or a technical barrier, the fact that it was very hard to get at the molecule?

Hayes: Mostly technical. Mostly rested on the fact that nobody could do very much at demonstrating this.

Hughes: I understand that Gofman's use of the centrifuge in lipoprotein work was a breakthrough, that that had not been done before.

Hayes: Yes, that's why I think that probably he didn't have specific ideas about lipoproteins when he arrived at Donner Lab, because lipoproteins really weren't very well understood. A very big step in the understanding of this whole question was contributed, I think, mostly by Frank Lindgren, who has his office next door. Frank had the idea about understanding the pattern that you see in the centrifuge. You've probably talked with Alex.

Hughes: I've talked with Alex, but not with Frank.

Hayes: I don't know how familiar you are with the centrifuge pattern, and what it tells you.

Hughes: I'm not. I know there is one. [laughs]

Hayes: Okay. You put the serum into a centrifuge and spin it. The first and major thing that you see are that the molecules, which are generally more dense than the surrounding fluid, would move towards the bottom of the tube. They would be thrown to the bottom, and they would sediment. In this sedimentation, there were some very strange patterns right on the edge, and they were labeled as protein XYZ or something--not well understood as to what was happening. It seemed very strange. You'd put in different densities; you'd get different shapes of these edge patterns.

One of the big steps in understanding this was to recognize that what was happening is, you have a molecule that has a lot of fat, a lot of lipids, so it's not very dense. It tends to float much more easily than the albumen sediment. It would be a molecule that's denser than the serum by itself, but less dense than the serum plus the other molecules that were moving down the tube. So you have a molecule, then, that piles up right on the boundary. It's going to sediment in the pure--let's say it's water above the molecules. It's going to float in the material that has the other molecules in it. That was a neat idea. And I think that's what Frank's idea was.

Hughes: He was interpreting, then, what was being--

Hayes: Yes, you could interpret what these were. Clearly they are the lipoproteins. You could begin to separate them out. You could make a density so that you could separate these lipoproteins from the rest of the proteins. Now you could study them just as flotation patterns, and you could begin to characterize them on the basis of their rate of floating. From that you could learn things like their shape and molecular weight. So all of this grew out of being able to separate the different lipid molecules in blood.

Hughes: Which was Lingren's contribution to this experiment.

Hayes: Lingren's major contribution.

Hughes: And is that the stage that Gofman steps in?

Hayes: Gofman was interested, I think before that, in these patterns. I wasn't here, so I don't know the exact sequence of things, and I don't think Alex was here then, either.

Hughes: He arrived about the same time you do, I believe.

Hayes: I think so. Frank would have in his mind a history of what happened.

Hughes: Can you recreate it from your arrival on? Do you remember at what stage the project was in?

Hayes: When I was here, the patterns had been unraveled so that I could go to work reading these flotation patterns, and it was already understood.

Hughes: You mean the four densities?

Hayes: Yes. We weren't very far along on it, but there were already programs underway that would measure in different individuals the low density lipoproteins in terms of concentration in the serum of these people, and programs, then, that were taking that information and correlating it with the pathology or medical history of the person.

Hughes: But this was still a localized effort. It hadn't gotten to the national level.

Hayes: No. The cooperative programs and all of that, no. It was early, but the initial interpretation of the patterns had been made. And the decision to separate the lipoproteins from the other proteins in order to study them had been made already. At this point, then, it was just about the time when correlations began to appear between the low density lipoproteins and the coronary participants.

Hughes: Where were the samples coming from?

Hayes: They were coming, I think, from physicians that Jack Gofman contacted. Maybe some with Hardin Jones working on it, too. Jack Gofman and Hardin Jones worked together on these program.

Hughes: What was Jones' interest?

Hayes: Well, he was a physiologist, so he was interested in changes in the lipoprotein with physiology. One of the environmental or outside influences that changes the lipoprotein in serum is radiation, and that happened to be what I worked on in this. There had been an observation in rabbits that were irradiated that the serum became milky--so much lipoprotein or lipid that the serum would actually be milky. If you give a dose where about half of the animals die, you could look at the serum and tell which ones were going to die. So it was associated with lethal damage. I remember it was Hardin Jones that mentioned that this would be something that he'd like to learn more about. "Maybe you'd like to follow it up," he says to me. So we started following this up.

Hughes: Was this at all connected with his theory of aging?

Hayes: I don't remember that as that early, although there certainly is a lot of overlap between the two. But I don't think it came that way. I think it was later.

Hughes: Can you say something about the breakdown of labor? What was Hardin Jones doing? What was Gofman doing? What was Frank Lindgren doing? Nichols, you, who else? Maybe we should mention other people in the group.

Hayes:

Yes, there were several groups in the laboratory that worked with what would be the group leaders, I guess. There was Gofman. And Hardin Jones' was a separate group, although they both had some interaction with respect to lipoproteins. Then there was [Cornelius A.] Tobias. And John Lawrence[1] was also here. But I don't remember it being as much as a group with him, as that he was the director of the whole Donner Laboratory and dealt with the physicians that were coming to learn about nuclear medicine. The training of physicians that took place would be under John Lawrence's direction.

Hughes: But not day-to-day bench work.

Hayes: I would see him in his office. I saw him mostly with Jack Gofman, because that was the group that I was in. And in that group was Alex Nichols, Frank Lindgren, Dean Graham--he left shortly after he received his degree. Harold Elliot was in that group before I was. He didn't stay too much longer after I had come. Then there were people that were added to this group over the years: Bernie Shore was an important long-time contributor, and John [E.] Hewitt was here early on. John Hewitt and I worked together on many research projects. An excellent scientist.

Hughes: I would like to know a little bit more about Gofman as an individual, and also about what did happen. I know there were problems eventually--the atherosclerotic index business, and all of that.

Hayes: For one thing, I don't have a lot of the information because I tended to diverge from the story. And it always takes a little bit of time, I think, after the event, before anybody can look back and see what the perspective is. So I don't have a lot of the information.

I know some of the early days and Jack Gofman's personality.

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[1] See the oral history in this series with John Lawrence.

He is not, I think, terribly patient. He's devoted to excellence, and he's not terribly tactful. Now those qualities are some of the things, I think, that led to misunderstandings or to resentment, to difficulties on some of the cooperative programs. They're the same qualities that produced a tremendous amount of work of very fine quality that led the whole direction of looking at heart disease, and still does. You can pick up the paper still and there are people who are going to follow the molecular organization of the blood--people with such-and-such a doctor or such-and-such a prognosis of heart disease. So he really opened that whole thing up, carried it along a lot through those same kind of qualities. As a graduate student particularly, those are the qualities that helped you very much. You could say absolutely that he never wasted your time. A lot of time if you look back on the courses or even on the programs when you're in school, the ones that you enjoyed very much, though they were just a lot of fun to do, they wasted your time, which is a very big price to pay for having such fun.

So some of this had to do, I think, with his style. He had a cooperative program with a lot of different laboratories in the country. He had really started a lot of these techniques. They were going to run a program where they'd all look at the lipoproteins and be able to standardize their results. Well, no sooner did the program get started, then Jack Gofman and the people working with him--they already had a lot of momentum going on developing these techniques--they developed new techniques. so there'd be changes, and Jack would see it as a better quality way to do it. Some people in the cooperative program would say, "Well, we never got caught up with last week's change. How are we ever going to get these things standardized?" So then the results begin to come in. Some of the people have brought it up to a certain stage, and others to a different stage, and it won't correlate. And they say, "Well, you people are reading the data differently out there," and Jack Gofman says, "Well, it's because you people are incompetents back there. You can't do anything right."

As far as I can remember, the kinds of things that would irritate both sides had to do often with an impatience to be on with the improvement while the other side said, "We can't just keep changing all the time. If we're going to get some kind of uniform results, we have to stay with one technique." I don't know exactly how we could resolve that.

Hughes: What did this do to the morale of the group?

Hayes: I never saw the morale of the group anything but full speed ahead. The morale of the group, as I recall, was absolutely superb.

Hughes: Even with these external problems?

Hayes: Yes. There was a great confidence that even if we could recognize that they had some legitimate complaints, still, the place to be was with Gofman. He was the one that was leader of the field.

Hughes: I've heard it said that Gofman's students idolized him. Would you go that far?

Hayes: Maybe I would go that far. First, let me think about the group. I don't think "idolize" is right. I admired him professionally. I don't think I could idolize a professional relationship. He was good. I certainly admired him.

Hughes: But it does sound, from the two accounts now that I've heard, that it was not just the usual relationship between a graduate student and his supervisor or director. For one thing, it's not usual to work nonstop. [laughter]

Hayes: You have to look at the rest of the group, too. It's not solely the result of Jack Gofman's personality, but the morale of the group, and the work of the group. A lot of it was fed across as well as from up and down. The group worked through the night, and if Jack Gofman went to Italy, they still would work, even if they lost that kind of contact and direct kind of inspiration. I think it would depend some, too, on how people relate to the group. As I say, I'd come to school as I'd go to San Francisco. Some other people in the group may have a more personal contact with the group. I tend not to be very personal in my work. And others may find that quite a difference. They then are available to answer the question of whether the group idolized him. I tend not to.

Hughes: That's interesting that you should say that because in just reading through your papers, and I haven't read them all--[laughs]

Hayes: Thank goodness. [laughs]

Hughes: --but I thought the opposite. I mean, at least of the people that I've talked to so far, I thought there was more of your personality in your papers than--

Hayes: Yes, I almost said that at the end. I couldn't think how to say it. It sounded so convoluted. I'm only personal in a professional sense. That is, part of my profession is to be personal. That is, to bring in the value of the individual. But not me. The individual, that's always as if it's outside of me. That doesn't mean that I can't recognize or even work towards that, and write and say something about the value of the person. But I can be personal about my work, without bringing all of my person to it. I need to be there, for example, to experience that cell, not just to measure it, but to experience it. It's as if I were little and could go there. Poincaré, the French mathematician said, "It is by

logic that you prove, but by intuition that you discover." Well, that means you have to make an intuitive kind of appraisal. You have to be there with intuition as well as reason. But even saying that, it doesn't necessarily bring in myself.

Hughes: So you might go so far as to say that if you were in a different type of research that didn't require this person there, that it probably wouldn't be there.

Hayes: I think so, although I doubt that I would move into that research. I don't know which comes first.

Hughes: Yes, we're getting into a chicken and egg sort of thing.

Hayes: I'd probably moved into that because that's the way I like to work professionally. I think the word that struck me is "idolize". Even though I deal with a personalized approach, and a personalized evaluation of even Jack Gofman, it would have to be personalized outside of that area. I don't idolize somebody professionally. It's very hard in my mind, to work this out. We're back to the beginning of our talk, where I said we would sit around at home, but we didn't sit around discussing the actual things that we were talking about. You need some conversational framework. That's the only way to teach. It's part of what I learned in teaching in a fine arts school. If you want to teach something that's as difficult to teach as fine art, I think you have to recognize you can't put it in a list on the blackboard. You somehow have to sit down, a lot of time goes by, and people come in and they work and they paint and they discuss their painting and talk. And you somehow learn from the artist. And so for that kind of quality, if I said I idolized somebody, it means I've had a chance on that level of long-term nonspecific kinds of contacts, whereas what I'm saying here is a personal evaluation based on more of the qualities that I can contact. I didn't know Jack Gofman that well to idolize him. And I also would have to grow up with him or live with him.

Hughes: Yes, it was a strong word. It was a word that I used because somebody else had used that as a description, and I wanted to see what your reaction was. [laughs]

Thesis: Lipoproteins Effects Due to Radiation

Hayes: I worked a lot with John Hewitt on the lipoprotein effects due to radiation, and on some of the later electron microscopy. That was another thing that really came out of the lipoproteins. John Hewitt and I tried to visualize these large molecules in an

electron microscope. The centrifuge counter is nice, but it's also nice if you can use other techniques to show that, for example, the diameter calculated by ultracentrifuge analysis also compared with the EM [electron microscope] work. So we used to use the electron microscope in the basement of Physics. I guess it was the first one here. And then we got, very early, one of the first commercial [electron] microscopes. The people down at LSB used to come and use it. They had none in Biology.

Hughes: Could you visualize the different densities of lipoproteins?

Hayes: Yes, we could. We managed to see the lipoproteins and tell some of the characteristics.

Hughes: Had you kept this microscope idea in the back of your mind all along?

Hayes: I don't know that I planned it particularly, or consciously thought about it from time to time. But I liked it.

Hughes: Why Hewitt? It happened that you had started on the radiation effects, worked together. Was that the reason? I notice that for the first few years most of your papers are written with Hewitt.

Hayes: Yes. The radiation experiments really took two people because you had to check these animals around the clock. One person couldn't do it, and we didn't have any technical support. We did it ourselves. Did everything from the feeding of the animals to running the ultracentrifuge. If you have an experiment that has to be done on a time basis, that doesn't allow you to turn it off at night; you have to have two.

John was involved in extending the experiments we'd done on rabbits to the other species, and through that, to building up a library of what the lipoprotein content is in various species for experimental work. Then we both did some work on the electron microscope. That was just after our thesis work. I don't think our thesis had anything on the electron microscopy.

Hughes: What was the thesis work?

Hayes: That was on the radiation effects on lipoproteins and the ability of lipoproteins to predict lethal damage in organs, mostly studied in rabbits. It was aimed towards a better understanding of radiation therapy in the treatment of human cancer.

Hughes: Who else was on your committee?

Hayes: Gofman, Hardin Jones--. [pause] Well, let's see. I remember my qualifying committee. I had Robley Williams for electron

microscopy, but I don't think on the thesis there was any electron microscopy. Maybe there was. I have to go back and look at my thesis. Ernie Dobson was on my qualifying exam and maybe on the committee, too.

Hughes: Would you say something about Gofman as a supervisor? How much was he directing your work? How much contact did you have with him as a graduate student?

Hayes: Well, he was a very enthusiastic investigator, and this enthusiasm permeated the whole group. We used to meet every week for a group seminar. And they were very good. They were really vigorous, critical. He would take part in those every week, and with a great deal of attention. Each person would present one of these, and it would go around the group and then your turn would come again.

Hughes: Was it on the individual's research?

Hayes: Yes. What's your research? What are your results? And then they tried to see if there were holes in our results, or if there were some things you hadn't thought about that they could suggest.

He was in charge of a lot of students, with his own work in addition, so I wouldn't say I saw him a lot on an experimental basis in the lab for a lot of hours every day. John Hewitt and I pretty well worked on the radiation. I don't think we'd see him while we were working with the rabbits or working with the X-ray machine or any of that. He couldn't go to each of the experiments, but he used this weekly seminar. A lot of fun. He's one of the quickest brightest people who ever worked here.

Hughes: I got a distinct picture of an around-the-clock operation.

Hayes: It was around the clock, yes.

Hughes: Was that true of every group within the lipoprotein group?

Hayes: Yes. Every part, as far as I can remember went around the clock.

Hughes: Was there a feeling of distinctness from the rest of the laboratory?

Hayes: Yes. It's hard for me to say what was going on with the other groups, but the lipoprotein group was pretty much involved in the various experiments under Jack Gofman. I didn't have a lot of chance to contact some of the other groups, really not until I started on the electron microscopy part. Then the instrument happened to be upstairs.

Electron Microscopy

An Early Transmission Electron Microscope

Hayes: We could get this instrument at a very opportune time and price. Part of the Livermore Lab--it wasn't the part under the Atomic Energy Commission, but I think Standard Oil had a research program out there, at Cal Research. They were terminating that. They had a brand new microscope. And so Bob Souci, who was the business manager here, learned about that and came down and said, "Hey, you guys want to go out and look at it?" We went out and looked at it and brought it back.

Hughes: What was the resolution in that microscope?

Hayes: It was a very good microscope, and you could do most of the things you can do now with sections. You're limited more by the [specimen] section and by the preparatory technique than you are by the resolution of the microscope. For very high resolution work in TEM [transmission electron microscopy], it's the radiation damage of the beam more than the instrumental design that ultimately limited the resolution. The resolution was quite good. You don't see very much change in the operation of the instrument. Even the home-built instrument we used in the physics department was quite good. I could pick out a lipoprotein picture here, or even a section picture, if the section was prepared very fortunately, but particularly for the particles, where you didn't have to section. The ultra-thin section and the techniques that have gone into the staining and the histochemistry and preparation of the specimen--those are the things that have changed. The microscope has not changed very much since then.

Hughes: How did you prepare the lipoprotein?

Hayes: Well, originally it was a transmission microscope. There was no scanning microscope. [Pointing to micrographs on the wall] All of these are scanning microscopy. But in the transmission microscope, since you couldn't cut thin enough sections for the electron beam to go through at that time, you looked at what you could look at and those were the viruses--Robley Williams looking at viruses--and the macromolecules. Our kind of work with lipoprotein is an example of looking at a particle.

Hughes: Did you just dry them on a grid?

Hayes: Yes. The secret of osmium fixation of lipoprotein EM of lipoproteins at that time was to put in a particular fixative of

osmium tetroxide that binds the lipid and keeps the lipid intact. Otherwise it flattens out on the surface when you air dry them.

Hughes: Was that known?

Hayes: That wasn't known.

Hughes: You had to develop that?

Hayes: We developed it. At least we were there and we recognized what we did. We were trying different things. Walt Humphreys down in the Life Sciences Building was using the scope up here because there wasn't any microscope in LSB. He knew about a technique of using osmium for some of these sections that they were trying to cut. It was just about at the time of the development of the ultramicrotome that cuts sections that are thin enough to look through. So Walt was working with some different stains, and he came up one day and he said, "This stain, osmium tetroxide, looks like it might be interesting for you because it's supposed to stain lipids. It's supposed to stain fats."

Hughes: That was known from histological--

Hayes: That was optical microscopy at first, and then from his work where he wanted a heavy metal. What they did when they went to transmission electron microscopy, they wanted some stains. All the rich, specific stains that you have in a light microscope, you can't see as different stains in the electron microscope because they're based on molecular structure. And the transmission electron microscope really only sees atoms, atomic numbers. It depends on whether it's a heavy metal or not. It doesn't depend on whether it's an aniline dye or whether it's just a collection of carbon, hydrogen, or nitrogen of that same density--you'd see it as exactly the same intensity of gray.

So Walt was looking for stains to use that contained heavy metals, and osmium was something that he looked at. Then he mentioned it to me, and I said, "Why don't you bring up some?" So we tried this and it just kept these lipoproteins like they were ball bearings almost, so you could do a lot with them. The secret there was not that we developed it. That is, we didn't sit down and psyche out the problem. But we had a lot of contacts with different people, and one of those contacts said something and offered to try it out. And then to be in a position to recognize it, that it was worth grabbing. We do more of that in an active sense. The rest is a kind of passive thing. You throw yourself around and say, "What happens?", rather than moving along a plan.

Scanning Electron Microscopy

Hughes: There comes a stage when you began to lose your ties with the lipoprotein group, and you got more and more interested in microscopy, and particularly scanning electron microscopy. I'm not sure what the chronology is there. How did that go?

Hayes: I worked pretty much with lipoproteins, although I did a considerable amount of work to see that the electron microscope was available for people that could use it in biology. But I stayed, for my own research, pretty much with lipoproteins until about 1965. And then one of the young professors in electrical engineering came over and this was [R.] Fabian [W.] Pease from Cambridge, England, who was now here at Cal. He went first to Toby [Cornelius Tobias], and Toby then said, "Well, maybe you can see Tom Hayes about it." What Fabian had was a scanning electron microscope.

The instrument was again a daughter of radar, of the technologies that went into TV amplifiers, to be able to handle high frequency electronics. The basic idea of a scanning microscope, of having a time sequence of points instead of an image that focuses the radiation after it interacts with the specimen--that was quite old, and so was television. Both ideas were around in the thirties, but we couldn't make them work. Well, after the war at Cambridge University in England, they made it work.

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Hayes: They took an idea and brought it to the point where you could get very fine images--almost as good as you see here. Again, the instrument hasn't changed very much; we've got a lot of change in the preparative methods.

Well, in that group, not right at the beginning but fairly early, was Fabian Pease, who was British, and Tom [E.] Everhart, who was American and doing his Ph.D. work at Cambridge. After he got his Ph.D., Everhart went first to Westinghouse, I think, for a little while here in this country, to consider making a scanning electron microscope in this country, and then here to Berkeley. And when he came here, Fabian Pease came, too, to Electrical Engineering. They built a scanning electron microscope [SEM] here in Berkeley.

Hughes: When was this now?

Hayes: '64 and '65. Fabian then saw what he thought was a very exciting possibility for scanning electron microscopy. These images are

made with secondary electrons and they show you the distribution of matter in space. They show it to you in a way that allows you to look at the specimen instead of through it. They show it to you in a way that allows you to look at shape. It does that by having the secondary electrons come along as a function of the angle between the beam and the surface, which is a similar function to the shading code that tells you that my head is shaped like an egg. It's a single-eyed code. You close one eye, you can still tell that. It's because it's shaded on the sides. [Points to the electron micrographs] The reason we know those are spheres and not circles is because of the shading. It's not binocular vision; it had only one view, and so forth. But that was not Fabian's idea.

Fabian's idea was to use those same electron beams but instead of counting the secondary electrons at each instant, we would count visible light because very often, when electrons interact with matter, you get some visible light. Sometimes you get a lot, like the face of a TV screen. Electron beam hits that face, gives off a very nice bright signal. It works very well. Before I mentioned that when you work with electrons, you don't have all of these beautiful colorful stains, that specific histochemistry that you have with the light microscope. You gain with the electron microscope a lot of resolution, but you've lost information. And resolution is not the name of the game; that's not the goal in itself.

There's a kind of nice story in *Alice in Wonderland*. Alice is talking to the White King, and White King says, "Look off down the road and see if anybody's coming." So Alice looks off down the road and she turns to him and says, "No, I see no one." He says, "Isn't that remarkable? At that distance, too!" People come into our lab and look at all the instruments around and say, "What do you see through your microscope?" And sometimes being reasonably honest I say, "I see nothing of importance." And they say, in effect, "Isn't that remarkable? And at that resolution, too!" The recognition that resolution was not the whole story led really to the value of what the scanning microscope does. It can't see smaller things than transmission, but it sees them in different ways--not only seeing in the sense of experiential vision, but also sampling in terms of measurement, chemistry.

Okay, if you can get the signal to come off as visible light--visible light depends on molecular organization, not just on the atoms; it depends on the molecules. You could take the stains from fluorescence microscopy that you usually excite with ultraviolet light, and excite them with the electron beam instead, and maybe then have an electron microscope resolution almost with the high information associated with a light microscope--kind of the best of both worlds. That was Fabian's idea. That's called

cathodoluminescence. So we started to work on that. That would be a separation, then, from the lipoprotein research.

At that time, I was still pretty much part of the lipoprotein group. There were four of us: Alex Nichols, Frank Lingren, [Norman] Keith Freeman, a chemist, and myself. At about that same time, too, maybe it's a year earlier in '62 or '63, Jack Gofman left here and went to Livermore, so four of us were left in lipoproteins. Only a couple of years later, though, I started off on the scanning microscope. Went over to see Fabian's instrument. He was going to show me cathodoluminescence. But the thing that was so exciting to me was the secondary electron picture. In biology, in medicine, the secondary electron image was exciting. The SEM was fairly new, and in Cambridge it was developed in electrical engineering, and here it was in electrical engineering, also. At Cambridge they had kind of talked to some biologists occasionally, but it seemed to them in talking with these people there was not much application in biology for scanning microscopy because the resolution wasn't any better than TEM.

Well, it turned out that there was a lot of application. It has to do with what you need to know in biology--that you need to know, often, the connections between the parts, and that's very hard to maintain if you slice it up. No matter how small the parts are that you look at, or how good your resolution is, you've lost the contact between the parts. You need to know some other qualities, too. So it does have a use in biology. [Points to bookshelf] There's a series of books. The thinnest one on the left is the first of these scanning electron microscopy symposiums held in '68. I went there and I was the only biology person or biophysics person there. I gave that one paper. Now they have four volumes every year. Maybe two-thirds of it is biology.

Hughes: Were you the one that recognized the biological implications? Or had Pease already made that connection?

Hayes: I was certainly excited about it. I like to work with groups. I like an audience. I like to perform. And I liked this, because it gave me a chance not only to talk, but to show examples visually. I always liked visual kinds of information. But I have a great respect for the advantages of qualitative work. Of all the characteristics I think that you can say are related to biophysics--what is biophysics--I think you'd have to say it's quantitative. At the same time, you're dealing with a system that doesn't yield easily to quantification. We don't want to be in the position of measuring what we can instead of what we should. So I'm interested in extending what we can do with these two ideas: we need to be quantitative, and we need to deal with problems that are of significance in biology.

Well, this instrument seemed to me to be that instrument. It was just the kind of thing that you could do. Even in the first look at it, Fabian could list ten different signals that you could use to paint your image. It's as if suddenly the kinds of information were multiplied by ten, in the kinds of images that you could present. So that was exciting.

Some of what I'm trying to do is to say, "How does this fit into biology?" I don't think they were right in England when they said there's limited application in biology. I think there are many uses, but you have to let people know about the instrument. The people who need information are not always the same people that can produce the instrument to collect that information.

Hughes: And you were doing all this with the administration's blessing?

Hayes: Yes. This was under John Lawrence. All the way through the association that I had with the laboratory there was a very open, free kind of exchange. You could work on things that you found to be most interesting and productive. And generally there was considerable encouragement. That's a combination of things. It's a combination of the policy of the administration of the laboratory, and it's also a result--or it's at least strongly influenced by the economic climate that exists with the funding. If you have very big growth, lots of support, you can run a system that explores all kinds of possibilities.

Hughes: Wouldn't you say that the nature of the field itself, biophysics--which obviously is a melding of at least two disciplines--? The problems are wider, I would think.

Hayes: Both of those things are important.

Hughes: Also the fact that it was a new field and the limits were not well-defined.

Hayes: Not even known just where to go yet, so there was a lot of exploring. You're right, as the field gets more mature, you find that there are certain areas that tend to be recognized more as the formal discipline. I think that's happened to biophysics.

The Biophysics Enterprise at Berkeley

[Interview 2: May 20, 1980] ##

Hayes's Attraction to Biophysics

Hayes: When I came on as a physics undergraduate, I took some courses that were given in the biological side of physics. One course--I guess it was still at that time called Physics 126--it was the only course in physics that dealt with biophysics. It was a series of lectures. I think probably John Lawrence was in charge of that course. But it had, as I remember, a different lecturer each week. They would talk about their aspects of biophysics or of medical physics. I don't really have any remembrance of how the department was set up. It was, in my mind, part of the physics program. At that time, I would have thought it was truly a division of the physics department. As it grew later along, the connection with physics became much less clear. But at that time, it was a part of the curriculum of physics.

Hughes: Was that 126 taught exclusively by Donner Lab people?

Hayes: At that time, I didn't know Donner Lab. I only knew LeConte [Hall, location of the physics department]. Let's see, who did teach that? I think Hardin Jones--

Hughes: Tobias?

Hayes: Tobias, I think. I can't remember. And since I didn't even realize there was a building over there called Donner Lab while I was an undergraduate in physics, I don't really know. I found the course, Physics 126, very interesting because it opened up a whole area of physics that I hadn't really had a chance to explore before. It was an important course.

Hughes: But it wasn't really instrumental in getting you here eventually, because you explained how that was almost a fluke.

Hayes: Right, but it was instrumental in my thinking about biophysics instead of straight physics, so in that sense it was a key course.

Hughes: You haven't mentioned any particular biological leanings prior to that.

Hayes: No, I don't think much before that there was any serious thought about biological science. A little bit; I guess you kind of cover all the possibilities lightly. I think it was much more in my mind that it would be something like physics or engineering or

engineering physics. A good friend of mine was in engineering physics. I didn't know very many people in biology. Most of my friends seemed to be in architecture. I like architecture, but didn't have very much contact with biology. I liked it as a kind of hobby, a kind of naturalist approach rather than biological. And I did like the microscope as a toy when I was young.

Hughes: What was it that appealed to you about the biophysics? Was it the microscope that drew you into what became a career?

Hayes: No, not at all. I think it was much broader. I think it was probably that its connection with things that were alive was appealing, particularly at that time. I was finishing up in physics, and I'd been in engineering. It was kind of fun to see a different subject matter. The living system has a built-in kind of appeal to it.

Hughes: Was there still the sense of a new and developing branch of science?

Hayes: Yes, very much. It was absolutely brand new and that was attractive, too, compared to physics which was very well-established. So those were the two main factors, I think, that made me go into biophysics. First being the kind of warmth of the subject matter. Physics to me became more and more of a [pause] impersonal, cold kind of a physics. The machines were very big, and the approaches were very far removed from anything that could relate to a person. I think part of what attracted me to it was that I might help in a medical sense. So that's the kind of altruistic rationale for it. The other part is that it was an opportunity. Here you were at a place with a biophysics program when there weren't very many biophysics programs. Very few places could list an accumulation of people that were even close to what was here. So it was a combination of a practical look at what field was really taking off, and a kind of ranking of subject and of interaction in a personal sense, a sense of where you can contribute.

Someone once said that two things that really make a scientist go are recognition and a sense that you're contributing. I forget who said that. It's not the only two things, but they are two important things. And in both sense, the biophysics seems to be a little bit more of an open door than the physics.

Hughes: Would you say that Donner Lab was at the center of things? Donner Lab was where a lot of the radioisotopes had not only been first made, but their applications, at least to biological and medical purposes, in many cases, had been done here for the first time. Did a student have that feeling, too?

Hayes: I really went into biophysics before I ever heard of Donner Lab. Part of the reason that it is not easy to say is that there was very little separation between Donner Lab, the people that worked at Donner Lab, and the teaching unit, whether it's the Division of Medical Physics or the Department of Physics. Going through physics, I had that same feeling as a student, that there was very little difference between what was then the Radiation Lab and the Department of Physics or the Department of Chemistry. They were the same people essentially doing the same work, and I didn't perceive any difference. So it's hard to say, then, "Well, how do you see Donner as separate from the whole thing?" If we put them both together as "Berkeley", Berkeley was one of the big centers of biophysics, and there were only a handful. There's MIT, Harvard, and a couple of other places, but not very many. You definitely had the feeling that the center was here sometime.

I was already in graduate school in biophysics before I knew that Donner Lab existed. And then when I found out, it didn't strike me as something new that I was finding out about. It was just where the office was of Hardin Jones and Jack Gofman. I might have gone over to LeConte Hall if I'd learned that there was a position over there in biophysics. I think that shows that the unit didn't really exist as separate from the university. The unit grew as the academic side became more clearly defined and as the laboratory became more enlarged, somewhat separate from the university. It's still very close. You can look at any of the national laboratories; I can't think of any that can say they have that kind of a relationship that exists now between Donner Lab and the university.

Hughes: In the early days there was nobody in the Academic Division of Medical Physics that didn't also have an appointment in Donner Lab. Nowadays it's changing.

Hayes: The other was almost true, too. There was almost nobody in the lab that wasn't on the faculty. Now there is some difference--some separation in both directions. There are some faculty members in the Department of Biophysics who are not members of the Donner Lab, and there are a very large number of people in the Biomed Division [of Lawrence Berkeley Laboratory] that are not on the faculty.

Hughes: That hasn't always been.

Hayes: No, but I think it's not too recent. For example, all of the physicians that came to Donner to train and to work, none of those were faculty members. Just by the nature of slots that open during the year, the growth of the faculty is necessarily limited in size. There were quite a few people who were not on the faculty. One very prominent name in the history of Donner Laboratory would be Hal [O.] Anger, who invented the Anger camera. And Hal Anger was not a faculty member.

Hughes: I've heard that there were physicians who would have stayed if they would have had some sort of university position, which was not forthcoming.

Hayes: Oh, yes. Well, I think you could find not only physicians, but almost any graduate of the program would probably stay if they could, especially these days. [pause] In the early days, this question of the academic association was not felt as strongly, partly because many were people who were established in other fields who came to Donner for special training. Physicians very often would not be terribly concerned about that, albeit if they wanted to stay a long time they might. And the other area is that in those days, there was much more of a growth environment in the scientific activities that the lab and the university were involved with.

Hughes: So it was really strictly a matter of money?

Hayes: No, it was not money. There was plenty of money, but it's a matter of the university's structure and policy and balance between different departments. The university has always, I think, tried to maintain a balance among all their departments--all the checks and balances so that, say, a professor of a certain rank, no matter which department he's in, whether it's popular at the moment or not, gets the same salary. And they all go through the same review process. People are chosen by a certain process; whether it's the best or not, it is the established process. It is not the same kind of process that you would use if you were in, say, an industrial environment, and needed engineering help. You would try and find that help as rapidly as possible, whatever the market price is. There's a set of characteristics about the academic side that were, I think, much more the determining factors than money. Many of the people then stayed without the academic appointment because the money was still what was there. That, too, has changed. Suppose you said, "Well, what we want to do is to build up a large staff outside the university;" if they said that, there's not that kind of a growth funding available.

Hughes: And then there's the problem of space, which seems to have arisen very soon after the division was founded.

Hayes: Well, that's true. I think if you have a program or a series of programs that are growing very rapidly, the people that are supporting it say, "Fine. Here's the money to get started." But you can't change a couple of things very rapidly. You can't build buildings very rapidly, so you tend to get crowded. You tend to say, "Well, yes, we can hire somebody, but where are we going to put them? Well, we'll divide up that office and that way we'll have more and more people, closer and closer." The space is always one of the things much slower to change than the initial thrust of the program. And the other is the kind of academic association that sometimes takes much longer than the personnel hiring. So those two things were both important. The space usually was just simply bent. I don't know that the space in the days of this early very large growth ever inhibited the hiring of these people, but it's certainly important now. There is a limit to how crowded people get and can still function.

Hughes: Do you know anything about how the medical school is reacting?

Hayes: No, I don't know much about that at all. [interruption]

The Interdepartmental Graduate Group in Biophysics and Medical Physics

Hayes: When I was serving as chairman of the Graduate Group in Biophysics--the group in biophysics extends across both campuses--there were no problems in the sense of friction between the San Francisco campus and this campus. There were routine problems, administrative problems, but no problems that deal with philosophy or personalities.

Hughes: How does the group relate to what is now the Department of Medical Physics and Biophysics?

Hayes: The group gives the graduate degrees and the department gives the undergraduate degrees.

Hughes: Oh, it's as simple as that.

Hayes: The group is made up of about twenty-six departments, with maybe as many as 100 faculty listed in the group, but the working group is considerably smaller in terms of faculty. Still, it's a very broad-based group. They offer the Ph.D. in biophysics, the

master's in biophysics, the master's in bioradiology, and the Ph.D. in medical physics.

Hughes: Does that take place mainly at the medical school, that latter one?

Hayes: No, that is mostly here. They're usually finished with medical school. The degree is designed for people who already hold the M.D., so it would presuppose that they have their medical background. It started really for people in isotope work.

Hughes: You were chairman of that group for one year--1977?

Hayes: Two years.

Hughes: 1977, 1978?

Hayes: Yes.

Hughes: What is the role of the chairman?

Hayes: Well, the chairman presides over the executive committee. The executive committee is elected by the group at large. The group at large meets every other year, and it elects the executive committee. The executive committee then meets and elects the chairman of the executive committee. The executive committee sets the curriculum requirements for the degrees. They check to see that necessary testing goes on, the examinations. The chairman works with the dean of the graduate division. The group is a graduate group and is responsible directly to the dean of the graduate division. So the point of contact then between this group and the graduate dean is the chairman of the group. Now within the group, the largest single department is the Department of Biophysics. The faculty in the Biophysics Department supervise over half the graduate students easily in that program. So there is necessarily a coordination that should take place between the chairman of the group and the chairman of the department.

Hughes: The chairman has always been a Department of Biophysics or a Division of Medical Physics person.

Hayes: Right, and now it's part of the by-laws. The chairman has to be someone from the faculty of the Department of Biophysics.

Departmental Status

Hughes: What about the very recent step from division to department?

Hayes: Well, I think that was very much in order. It kept the name in line with what the actual function was. For quite a few years the division was not really a division of physics. The term "division" implies that it's a division of something, and it was no longer a division of physics. As I say, when I took my course, it was really a part of physics, when you saw it as part of the physics department. But for quite a few years before this change of name occurred, the division had essentially operated as a separate department. [interruption] So I think that was very good. It brought the formal listing of the academic unit more in line with how it functioned. It came to be an addition to the College of Letters and Sciences. It's under the Dean of Biology whereas physics of course is physical sciences, so it was clearly separate. And the chairman of the division really operated in the same role as a chairman of a department. It became more and more autonomous as it went along.

Research Emphases

Hughes: And that was a matter of growth, and doubtless a difference in emphasis as far as subject matter is concerned, too.

Hayes: Yes, somewhat. It grew to include radiation biophysics, but other biophysics, too. And it grew towards the academic and away from the clinical.

Hughes: Can you explain that?

Hayes: Well, we're not a professional school at Berkeley, so we would not really fit in as a clinically oriented teaching unit. We don't have that kind of role to play.

Hughes: Although there were efforts on the part of Donner Lab people during that long controversy over where the medical school was eventually to be located.

Hayes: Yes, it's still going on. There still may be a medical school.

Hughes: If the medical school had ended up on the Berkeley campus instead of San Francisco, do you think it would've swung things the other way? I mean, towards the clinical rather than towards the biophysics research kind of thing?

Hayes: I doubt it. You have two things: you have the director of the Donner Laboratory, a physician, but you also have a group of people that grew up around it, and they are very heavily oriented towards nonclinical. Jack Gofman was, it's true, an M.D. as well

as a Ph.D., but he was first, in chronological order, a chemist. Toby is a physicist. And the program gave a degree in biophysics. The one degree that they gave in medical physics, Ph.D., had the prerequisite of an M.D. ahead of time. So you don't find any people growing up through that program. Those are people who have re-entered. They're a special group.

The initial group of people--John Lawrence, Jack Gofman, Hardin Jones, and Tobias--three of them are not medical, not basically. And then the people that came through the degree and for the first few years at least tended to stay and to influence the direction were people coming out of a degree program that gave a degree in biophysics. So I don't think even if the medical school were over here, biophysics would have become a medical program.

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Hughes: In many cases there seems to me to be a mixture of both basic research and applied research, or clinical research, whatever you want to call it. I'm thinking now of the early lipoprotein work, which of course involved a lot of basic research, but eventually, and with encouragement from Gofman, became very applied. And the same certainly is true now of the heavy particle therapy, which again had and still has a heavy basic research component. What about the tensions there? There must be decisions made at some stage: "Well, we've got something really good here. Should we accept more patients? Should we really push this? Or in so doing are we sacrificing the scientific aspect of it?" I'm putting it very simplistically.

Hayes: Yes, I know. Those are questions that must have been faced. There are still programs--my own program. Dr. [S. Jacob] Bastacky is a physician and he brings in much of the clinical connection that's so important to the program. At the other end, we have scanning microscopy--engineering people who are much more related to the instrumentation--and we have people who are involved in image processing or in structural relationships to basic biological questions. So there still is this kind of discrepancy. Toby's group has heavy interaction with radiation therapists and all kinds of really very clinical applications.

I don't know what the particular factors are that would have made those decisions move in one direction or the other. One, it seems to me is the fact that the medical school is in San Francisco. One of the important connections is the teaching hospital that goes with the medical school. The teaching hospital is not here on this campus; it's on the other campus. And whether that's right or wrong, that's the fact of it. Even if someone had said, "Yes, let's make this into a clinically oriented program,"

it would be very difficult. Besides the fact of the teaching hospital, in any kind of research program like this, maybe the most important resource are the students. And if you have a research program, let's say it was in clinical medicine, then it would seem to me that you'd have to have a program that gave the M.D. degree. People would feed into that; work with the investigators.

That wasn't the situation. The degree was a biophysics degree. As the students are drawn into that, they in turn interact with the research, and they tend to move it in one way or the other. I don't know how much the people involved might have wished one way or the other, and maybe even worked very hard one way or the other, but I think it was almost inevitable, given the physical environment, the academic environment, and the student source, that it would move more towards basic biophysical research.

Comparison of the Laboratory Scientist and the Academic

Hughes: What about another relationship--one that we touched upon--that between Donner Laboratory, a research institute largely federally funded, and the division, now the Department of Biophysics, a university organization? Were there tensions in wearing, so to speak, two caps? The federally-funded researcher and the state-supported academic?

Hayes: Yes, there were tensions. There are always questions that would be seen in a different light by the academic group and the laboratory research oriented group. If those two groups are represented in a single individual, I think there would have to be some tensions. In the early days it wasn't as common because there wasn't any clear separation. Perhaps those are the easiest days to live with in that there weren't these separate entities. In those days it was not very much different than any grant that's given to a professor in any department. That generally hasn't provided too many problems, at least problems that would make it not a workable system. So if someone in English or someone in zoology gets a grant from NIH, they have certain responsibilities to the federal funding agency and to the university. But that doesn't seem to be a great problem.

Some of the problems arose because of the very rapid growth and just the physical size of the unit [Donner Laboratory] that grew up that began to be seen, and rightly so, as a very, very big operation. There were those who then said, "Well, what we should do is just go right ahead and make it as big as we can." And,

"These academic people are getting in our way." And the other side, they were beginning to be developing people who'd say, "That great massive thing [Donner Laboratory] is really just reducing our quality, and trying to do a job that they are not set up to do." So there must have been tensions. I don't remember very many circumstances in my research where I had to decide one thing or the other as a lab person or as an academic. There are many common goals. You've mentioned that you might put me in the camp of the academic. I'm not really. I'm really in the laboratory, because my formal association is with the laboratory.

The Adjunct Professorship

Hughes: What does the adjunct in your title mean?

Hayes: The adjunct means that there's been a review process, and that's essentially the same as a review for any faculty. That implies that this review process has certified to some level of accomplishment, and it allows the contact with the students then to be on a better basis. The university has a responsibility to each of the students to see that the student has access to a faculty that has some level of competence. Everybody makes mistakes and it's not a guaranteed thing. The adjunct also means that the person is non-tenured and non-ladder-track. The person would not move to something else and up to a tenured position. It means that the teaching load is less and that the evaluation is based more on research and less on teaching. I am paid on a course-by-course basis, or at least quarter-by-quarter. So it's not a continuing commitment. It is not necessarily continuing in terms of support. Professionally they say, "Yes, that's it, you've got that. That's your review; it's all set there. You can't take that away." But it is not the same kind of commitment that can come with a tenured position. On the part of the adjunct, he doesn't contribute as much to the department in terms of committees and administrative role and teaching.

There are three classifications that involve people within the lab. There's the regular faculty. Second, there are the adjuncts, and I guess there are only a couple that are adjunct. The other is the professor in residence--a teaching load that is comparable to the regular faculty, but with a somewhat different support structure. And there are also some professors-in-residence appointments in San Francisco. In the laboratory there are now two classifications of senior staff. There's faculty senior scientist and staff senior scientist. I'm a staff senior scientist. A faculty senior scientist is seen as a person who would look principally to the university for the responsibility of security

of employment or any of the many things that go with that, whereas the staff person looks principally to the laboratory--that's a distinction.

The Multidisciplinary Approach

Hughes: Donner Laboratory was set up to be a multidisciplinary institution to cut across departmental lines. How do you think that has worked?

Hayes: It has been a smashing success. It has been one of the great things about Donner Lab. It brought all kinds of people together and there was a feeling that it was necessary to bring these people together without a lot of constraints. The thing to do was to get people so that they could do what they do best and not try and plan out a whole lot of things that you think they could do best. That, I think, has worked out very well. While it is maybe one of the greatest strengths, it's also one of the problems with Donner Lab. If you bring a whole lot of multidisciplinary people together, you get a great diversity of projects and you begin to lose any central feeling for Donner. But overall I think the interdisciplinary nature has been great. All the way from the clinical people to the mathematicians, physicists, engineers, all kinds of people. It's worked out very well.

The Laboratory Directorship

Hughes: Well, that leads me to wonder about the man [Edward Alpen] who is and the man [John Lawrence] who was director of the institution. The institution was founded by a man with predominantly clinical interests, although definitely with research interests, as well. You now have a man who I would say is more research-oriented than anything else. What has this meant to the institution along the way? You can't separate the institution from the director or vice versa, really.

Hayes: There are definite signs of those kinds of changes. There was more emphasis on the clinical when John Lawrence was director and actively involved in the laboratory. But even at that time this laboratory was part of LBL. It wasn't LBL then, but it was part of Ernest Lawrence and his programs and projects. I think the fact that John Lawrence came out to join his bother in essentially a physics department, physics activity, showed his interest and his enthusiasm for the basic research. So that even under the clinical

director, there was very much basic research going on, and it was encouraged very much. There was never a feeling that this [Donner Laboratory] was primarily clinical and tolerated some of the basic research. While John Lawrence always was very involved in medicine, he also was very encouraging on the other side. When he would be introducing what the laboratory was about, suppose there was a group of visitors: he was always very complimentary and enthusiastic about the basic physics.

Then as you come up to today, even though it may be a more research-oriented individual, there's still a great deal of enthusiasm for the clinical. The directors have changed and there has been some change. I'll say that there's less direct--well, I don't know, maybe not. There may be as much direct clinical work going on here today as when John Lawrence was here, maybe more.

Hughes: You mean proportionately?

Hayes: Yes, I mean as a proportion.

Hughes: John Lawrence didn't step down until 1970. How do you think his style of directorship suited the changing circumstances, i.e. a laboratory that was no longer a handful of hand-picked men? How did his way of handling things adapt?

Hayes: Well, I think the very great freedom that was allowed to the investigators paid off, and that's something that was not really affected by changing circumstances. By the time that his directorship was coming to an end, it was clear that circumstances were changing. Not only was the laboratory staff different and the professional nature was different, but also all kinds of changes--changes in funding, changes in how research priorities were determined. How were grant proposals reviewed? How much of the complex organizational information that's gathered here is effectively transmitted to Washington, say? How much is looked at back there in a way. Or that helps the people who are involved in trying to integrate the laboratories of the national system without overly restricting local management? So those things did change without any doubt.

It's hard to say what the director would've been if he went on just forever. It's possible that his style of directing might have changed. It's awfully hard to say, but I suspect that it probably would not have changed. He would still operate pretty much on an individual basis with not too much interaction with the Washington arrangement. These kinds of changes in directors you can mimic in the larger laboratory [LBL], too. And you could say what would've happened with Ernest Lawrence and his style if he'd gone on, or [Edwin M.] McMillan if he'd continued. What was the difference with [Andrew M.] Sessler coming in [as LBL

director]? Well, some of it has to do with outside forces. Some has to do with the person himself that comes in. And it's very difficult to say.

Hughes: Despite this freedom to pursue the line of research that the individual wished, was John Lawrence keeping his finger on what the individual was doing? How extensive was his knowledge of what, maybe not an individual, but a research group was doing?

Hayes: Well, I don't think any director can know all the technical details. And John Lawrence was not a pure physicist or chemist, so there were bound to be some blanks. His interests, too, lay in the application of isotopes in nuclear medicine, in radiotherapy, in a variety of fields that did take up quite a bit of his time. I think, always, he knew very well the activities in laboratories that would be necessary from the director. Some administrators are more physical scientists than others, and some are more MD's than others, and John Lawrence was very effective in combining both aspects. I think he knew quite well what the activities were in the laboratory from an administrative standpoint. From a technical standpoint, no one could know every detail. It depends, too, on the style of your administration. If you are essentially by yourself contacting all of these groups, that's a very difficult thing to try and do. If you have another level of people that will report to you, and they'll look into the individual details, that sometimes is possible.

Hughes: And the latter was his style?

Hayes: No, I think he tended to contact people himself, not to have many lieutenants.

Hughes: What, then, was the role of the assistant director? There were two assistant directorships that were held many years by Hardin Jones and Jim Born[1]. Jim Born was basically in charge of administrative details, and Hardin Jones in charge of the research program. Did it in actual fact work out that way?

Hayes: As I think back, Jim Born had several roles. I didn't have very much contact with administration at that time, so I don't know how effective that was in spreading the administrative job. Hardin Jones was involved with his group in his research. I don't know how much he was involved in directing other groups, other research efforts. And I don't know how often they'd sit down and say, "Let's look at the plan for the laboratory and research."

Hughes: Do you know why that position was created?

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[1] See the oral history in this series with James Born.

Hayes: I don't. I think sometimes it was not a very accurate description of what Hardin did do anyhow.

Hughes: The only thing that I've come across that might imply duties of that nature is in connection with Crocker Laboratory after [Joseph] Hamilton died and it was left virtually without a head. Pat Durbin[1] would report to Hardin Jones about her research program. But it was a very, very loose arrangement.

Hayes: No, I don't really know whether part of the role that Hardin played was in respect to Crocker.

Hughes: What about Hardin Jones--Hardin Jones as a man?

Hayes: I had a fair amount of contact with him all the way from the graduate student days. I had many talks with him. He was a most considerate and perceptive person, and I've always considered him as a friend of longstanding. I don't know enough about the research side to comment on the significance of his research on aging or on the question of drugs, but his physiological research was excellent. I've lectured on the SEM in some sections of his class on drugs and other topics in human biology. It was certainly a very active class. A lot of students would rise to criticize what was going on, or to support. His original research, when I first came, was much more physiological, with work during the war with the exchange of gases, and then the association with the lipoprotein program. In those days it seemed to me that he and Jack Gofman were very effective in making the lipoprotein program go.

[Interview 3: May 27, 1980] ##

Hughes: Dr. Hayes, you were going to continue with Dr. Jones, and specifically with the division of labor in the lipoprotein group.

Hayes: Some of that division, I think, was made on the basis of Dr. Jones being basically a physiologist. So, many of the more biologically-oriented questions would fall under his direction. As I remember it, he handled some of the medical questions that would relate to clinical changes resulting from altered diet, or changes that would be made in the serum lipoprotein level in an individual, whereas Jack Gofman was more concerned with the physical chemical properties of the lipoprotein molecules. Although Jack Gofman was an M.D., I think his first training in chemistry and his interest in the chemical side was evident at that time. I think Hardin Jones worked on some of the questions of resorption of plaques, changes that you'd hope would come about it you did lower the bad

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[1] See the oral history in this series with Patricia Durbin.

lipoproteins.

Let's say you're working with a basic assumption that the lipoprotein levels, of the low density lipoprotein at least, are a bad sign, and you can correlate that with people who have heart attacks. Then I guess the question was, "Well, suppose you reduce that?" And you could reduce it with diet and certain treatment regimens. If you do reduce it, what happens to the narrowing of the arteries, and the general atherosclerotic problem? I think one of the ways that you might get an idea on that was this lesion that occurs in the skin. I think it's called xanthoma. You could watch those xanthomas, which are fatty deposits, too, as a kind of exterior sign of what's going on in the arteries themselves. I think Hardin Jones worked on that side of it for some time.

Hughes: Did you maintain a close enough contact with Hardin Jones after you more or less diverged from the lipoprotein work to say any more about his later research? I'm thinking about the theory of aging and then his interest in drugs.

Hayes: I didn't really, no.

Hughes: No.

Hayes: Ah, I would, sometimes. We would get together in his class. He had taught a class in human biology, and if there was a place for some of the scanning microscope pictures and images, we would get together on that. But I didn't have very much contact. And in research we didn't have very many contacts.

Hughes: What about his impact on the lab as a whole? We talked about his role as scientific director. Were you aware of his influence in the more general sense on the direction of the lab?

Hayes: Not really. I'm afraid I had at that point pretty much gone to the scanning electron microscope, to the idea that I'd like to pursue the application of this particular form of investigation and even with respect to transmission microscopy. There wasn't a lot of time for transmission microscopy, and even less for continued work on lipoproteins. Although for several years there was a group of us here at Donner that were lipoprotein. Some of the lipoprotein people went with Jack Gofman to Livermore. Four investigators stayed here: Nichols, Lindgren, Freeman, and myself.

Hughes: Did you consider going to Livermore?

Hayes: I did. Yes. Jack Gofman asked if I would like to consider that and I did go out and talk to the people there, looked at that over quite a few months. There was naturally a very fine opportunity in terms of instrumentation and in terms of the nucleus of people

that would work on lipoprotein and on the elemental analysis that Jack Gofman had started.

Hughes: So that is why he was going? It was really to continue the lipoprotein work?

Hayes: And the elemental analysis. About that time and for several years before that, he began the work on looking at the trace elements in serum, and to tackle this from a chemist's point of view. Instead of looking at one disease in one element, let's get a look at the whole library of elements that exist in serum. How could they do that? They went to X-ray fluorescence as a method that would give this. And then do your correlation and see what diseases come out of this, instead of working with the disease and finding it from that direction. That was, I think, very exciting for him. A lot of the equipment that went in at Livermore was X-ray spectrometers and associated equipment for that side of it, but some lipoprotein [research] was going to go on, too.

Hughes: Was the fallout question in the picture in the very beginning?

Hayes: Oh, I would think so. The lipoproteins and the X-ray fluorescence were more, in my mind, his individual research interests. But he was going to be the head of the biomed division of Lawrence Livermore Lab, which was then called something else--Livermore Radiation Lab or something similar--and that would carry certain activities that were not his previous research emphases, but were part of that program. I would think that fallout distribution and all of that would be part of that. Some of the people that he gathered to go to the Livermore site--he took some people that were actively working on the X-ray, he took some of the lipoprotein group that had either been here--I'm not sure of anyone who was here still, but many had left here and gone to other places, then joined him at Livermore. Bernie Shore and his wife worked with lipoprotein. I think Russell Bjorkland. Three or four. So that was part of it, too. Then also he had people like Art Tamplin. Art Tamplin had left here, too, and gone to RAND and been more involved in this evaluation of worldwide fallout and things like that. I think right from the beginning part of what that division of the Lawrence Livermore Laboratory was involved with was to build up a good program to evaluate fallout.

Hughes: Why did you decide not to go?

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Hayes: Well, I think the reasons that would be attractive is the start of a large and active program out there.

Hughes: There had not been much biology and medicine prior to that?

Hayes: I don't think there was. I think Gofman was the initial biology and medicine director--associate director. I could be wrong on that, but it seemed to me that it was a kind of new thing. A lot of equipment and a lot of very useful instrumentation was coming in at that time. There was a gathering of very good people in lipoprotein and in the X-ray elemental analysis. So those were attractive reasons.

There were some things that were not so attractive. One is the distance; it is removed from any campus. Also you can't be two places at once. So if you go out there, you have to stop what you're doing here. I think that was probably the main reason. I had to decide whether to continue research here or at Livermore. And I think when it came right down to it, I felt I wanted to be at Berkeley.

Lipoprotein Research

The Diet Table

Hughes: When did the diet table come into the picture?

Hayes: Oh, I remember that quite a long time back. They used to have it at Cowell Hospital [on the Berkeley campus]. They'd have diet table, and this must have been in the early fifties. Several groups of people would be on these special diets. Some were lowfat, some were low cholesterol, some were lowfat and low cholesterol. There were always stories that filtered back about the way that people would react to theses different diets. "Always," they said, "the hardest people to manage were the people on these lowfat diets or zero fat diets." Very grumpy. It just doesn't make a person feel very comfortable. The meal doesn't satisfy. They were always very hard to get along with. At the next table was the ordinary diet, or maybe a high-fat diet. To those people, everything was just fine. [laughter] No trouble at all. And then from some of those diet studies, Jack Gofman took part in the book, *The Lowfat, Low Cholesterol Diet* that came out. I think that was an interesting tour into the kind of book that was meant more for the lay person.

I didn't see very much of the clinical side at all, or the nutritional side. I don't think I ever actually saw the diet tables in operation at Cowell Hospital. I'd heard how these were going. Since our research projects deal with lipoproteins, we'd sometimes see some of the samples that would come from the people. And some of the M.D. students that were here at that time, who

would also be part of the graduate student pool, and we'd talk with them.

Electron Microscopy

Hughes: How close was the information flow between what you were doing, which fairly soon because visual--I mean the electron microscopy of lipoprotein molecules--and the biochemists? Were you running to the biochemists and saying, "This is the molecule you're giving us, and this is what we're seeing in the microscope?" Was there a lot of exchange?

Hayes: Oh, yes. I think the only separation might be at this thing of clinical versus research. Probably it was more appropriate not to have graduate students in a clinical situation. I think that's the only kind of separation. That, as I say, results from the particular requirements of a clinical study where there are patients involved. That would naturally be set aside as something a little different, with the patient's privacy and best interests really coming first.

But then there was all the rest, all the research, and that was really very well integrated. We didn't think of the other graduate students, [as either] biochemists or biologists. A lot of times I didn't even know what they were, or whether they were physicists. We had a very, very effective series of seminars every week. I think everyone in that group pretty much thought of themselves as people working on lipoproteins first. Some of the people I didn't even realize were physiology graduates or some other discipline. So we didn't take our things usually to, say, the biochemist, and say that this is what we need to know about this. Within the group there were biochemists and they would present their information at one of these seminars that would have a very heavily biochemical approach. Next week, it might be a spectroscopist, or somebody working on viscosity, or it might be a clinical M.D. report--very much, though, an identification with the lipoprotein work.

I think there was a feeling that this was an important direction that was opening up to look at this particular disease that was and still is a very prevalent disease as a molecular entity. These molecules in the serum might have a direct effect on this disease and we might be able to affect them and through them do something about the disease.

Hughes: Were you actually the first to visualize--?

Hayes: The lipoproteins?

Hughes: The lipoproteins.

Hayes: Yes, I think so.

Hughes: And that was because of your use of the osmium tetroxide--

Hayes: Yes, yes, that's right.

Hughes: --which had not been so used prior to that?

Hayes: No, there hadn't been very much looking at molecules with high lipid content, with a lot of fat in the molecule. If you want to call the viruses a molecule, too, the viruses and large macromolecules were mostly high protein, and they were a little more durable for electron microscopy. You can dry them and they retain their structure pretty much, even against the surface tension forces of the liquid being dried.

But the lipids were not that way. If you dry them in air without some kind of a chemical fixation, without some way to make them very tough, you couldn't see them. They would spread out on the surface. We still don't know how much of that is surface tension, how much of it has to do with the fact that they are perhaps close to a liquid drop or a semi-liquid drop. Maybe just the surface tension of the substrate, once you get them out of a liquid, maybe that's enough to flatten them out. Even with freeze drying, you might still get in trouble. So for our first attempts we couldn't really identify the lipoproteins at all; we just couldn't see them. But then once that osmium technique was developed, then they were quite readily seen as the spheres, the appropriate size, and you could check this.

Hughes: And you could actually identify the different sedimentation classes.

Hayes: Yes, you could correlate with [them]. I think the best way to find out what the sedimentation distribution is in an ultracentrifuge. It still is, and it was then, too. But there were some things that you can't do with a sedimentation pattern. You can't tell, for example, very well what the heterogeneity is, how much different are individual particles one from another. That was one thing that was useful. Besides the sedimentation coefficient, there were models for axial ratio, length versus height, those kind of things that were obtained from indirect methods. And it would be nice to check them against a somewhat more direct analysis, so those were useful parts of the electron microscopy.

At that time, the fine structure was not really available to

us, not nearly to the extent that it is now with Dr. [Trude] Forte using negative staining. She started the negative staining approach, and that shows you some of the fine structure of the individual particles. But there were some useful things also from the entire particle visualization. For one thing, if you visualize it, people tend to be more convinced of the reality of this. The physician who has not been exposed to the indirect biophysical techniques is not very used to looking at centrifuge patterns and saying, "That must be a molecular species because the peak is nice and sharp." To him, it isn't very convincing. People that aren't used to those indirect methods are much more convinced by visualization. If you show a picture, people tend to say, "Oh, yes, I see those [particles]."

Hughes: So did you as a group use the micrographs in somewhat of a propagandistic way at time? I know there was a lot of public speaking going on. Gofman, Nichols--

Hayes: Yes, there was a lot. I think by the time we had the micrographs, most of that had settled down. I don't think that the micrographs would show very much more than to assure the kind of contact that would make the person say, "Yes, I see what you mean." As far as the real questions that were being argued, how to fractionate, how to measure the sedimentation velocities, those are the real questions that got to be so bitterly contested. Those you can't really throw much light on by an electron micrograph. We would use these mostly for studying the properties of these particles on an individual particle basis.

We began to be interested in why the osmium did such a good job of holding the shape of these high lipid materials. Osmium was used in section work in electron microscopy. It's a good dense stain, and it was being used more and more. The question was, "Where does it go?" You'd see a line of osmium, and you'd like to know, "Well, does that represent a lipid membrane or does that represent the proteins on the outside of the lipid?" So we were then drawn more towards trying to understand how the lipid and the osmium interact. How does osmium tetroxide interact with the lipid? And we used then some of our elemental analysis techniques to determine how much osmium went in per unit of lipoprotein, that kind of thing.

Hughes: When you say 'we', you mean you literally were involved in that too, as well as the electron microscopy?

Hayes: Yes, that was an electron microscope question. You can measure the amount of osmium directly in the scanning electron microscope. But there were some other electron microscopists that were interested in this. Jack Hershfeld was at Cutter Labs and was interested in this problem of where the osmium goes.

Hughes: When did the negative staining come in?

Hayes: Negative staining came in a little bit later. Negative staining of viruses was the first application, I imagine. And there you could begin to see the small unit substructure.

Hughes: Did that become the stain of preference at that stage?

Hayes: Yes, it shows you a different kind of information. If you want to know the particle diameter, say, and you want to determine the statistical spread of diameters and compare this to the spreading of the centrifuge peak, that kind of thing, I think you'd still use osmium. But if you want to know the surface structure of the lipoprotein particles, then you'd use negative staining.

Hughes: When a technique is still very new, say, the osmium technique, and you're doing something rather precise like measuring molecular dimensions, how do you have some assurance that you're not just measuring one artifact after another, that the molecule hasn't shrunk to half its normal diameter?

Hayes: You don't. You usually do an internal control kind of system, so that you say, "All right, I'll look at the low density lipoproteins, the high density lipoproteins, and the chylomicrons, and I'll treat them all through the same process. Then I'll say when I'm finished, that these are the relative sizes that I got between those three groups. You don't say that that's the size that it was when it was in the person's serum.

Hughes: Can you ever?

Hayes: Probably not, no. But I don't know for sure that you want to. What good does it do to do that? I think in biology sometimes that's been a little bit of a limitation--pursuit of fidelity rather than the pursuit of useful information. It's not necessarily true that you learn more from something that you've kept rigidly faithful to what it was, as compared to something where you let it deform, let it change, and then understand what the deformation process is. If you understand your artifacts, you can probably learn more than if you try and eliminate them. It's much like the artist and his painting. If he was limited to fidelity, he'd lose a certain freedom in representing the image. You have to have that plastic nature to it.

Hughes: It seems to go along with your idea of the importance of context in interpreting the object.

Hayes: Yes, I think that's true.

Hughes: "Context" being used in a rather loose sense here.

Hayes: It could be the preparative process, or it could be "context" in a more classic sense of what goes on around the molecule. But I think that's true.

Hughes: Do you find that idea acceptable to a scientific group? It does go against the classic image of how science is done, at least the layman's idea of science, where you isolate what you want to know, and you certainly try to divorce it from the context, from the environment.

Hayes: I think I found that most scientific audiences have a great deal of latitude in their acceptance of all kinds of ideas. They like to think about different ideas. I've always found them to be very courteous and interested and stimulated. Now the number that would say that he is right, that's really the way to go, I expect that's very small. It's more of an emphasis that might come about. It might be a little more occasional emphasis on context, more of an awareness that occasionally that is the direction that is useful.

I don't think I convert people. That's okay. I used to think, and I liked to say this, too, to the audience, that the people that disagreed with me were illogical if not irrational, but I don't think that anymore. Many of these questions in science have answers whose correctness cannot be judged on the basis of reason alone. Therefore, people who disagree with me are not illogical or irrational, they're just wrong. They pretty much say that to me. We don't expect agreement, but that doesn't lessen the enjoyment and the recognition that that other idea, that other position, may have some very useful things to say.

Hughes: Is there anything that should be added to our discussion of that early phase with the lipoprotein group and Gofman and Hardin Jones?

Hayes: Well, we've talked I think about most of the things that went into that. I think we should look back and see that while many of the things could be still argued and a few were proven later to be wrong, it started a direction that still goes on today--a way of looking at atherosclerosis in particular as a disease that has biophysical and biochemical components where you can tackle these, where you can do something about this. It's just no longer acceptable to say that it's just part of growing old. It will never be the same. I think Jack Gofman and the group opened some of those doors.

Hughes: Well, does that pretty well wrap up the lipoprotein business?

Hayes: I think so, yes.

Hughes: I was wondering if you had worked with Hal Anger, since you are

somewhat interested in instruments?

Hayes: No, I haven't had the opportunity to work with Hal Anger. He of course was very prominent in the whole program through the years. His instrumentation I have used as part of courses [which] people involved in nuclear medicine would present. We'd often in the courses take advantage of the proximity of all these people--not only in nuclear medicine, but centrifuge techniques and all of the people in the Donner Laboratory--to acquaint the students with some of the research modes that were currently underway. On these kinds of contacts, I would see some of the things that were going on, but I haven't worked directly with Hal Anger. The Anger camera and that series of instruments were probably the most well-known of the projects out of this laboratory.

Scanning Electron Microscopy

Pease and Everhart

Hughes: Now to Fabian Pease and the scanning electron microscope, which we touched upon in the first session. Could you say something more about your role in that work, and what the nature of your relationship is with Fabian Pease and that whole SEM?

Hayes: Well, Fabian Pease and Tom Everhart had a scanning electron microscope that worked, and it worked most of the time.

Hughes: That they had built?

Hayes: Yes. There weren't any commercial microscopes at that time, although they were close. As we said, they both had connections with Cambridge. Tom Everhart came back to this country and stopped at Westinghouse, I believe, and then he came out here, and then Fabian Pease came as a visiting professor. They built this scanning electron microscope. It was the instrument then that Fabian suggested we might apply to biological work. His thought was to use the cathodoluminescent mode, I think partly because he was very well aware of the comments of some of the early researchers in assessing what the role of scanning electron microscopy would be in biology. As we said, they had not been impressed that there would be very much use for this since the resolution wasn't as high as transmission electron microscopy.

I think what Fabian saw was that there are lots of other things that you could do with the scanning microscope besides see the secondary electron signal that gives you the shape of things,

gives you the topography or topology relationships. One of the things you can do is to use the electron beam to excite visible light in certain molecules. The TV system is essentially the same system of forming an image as is used in the SEM, and there you see the image because the electron beam excites certain fluors in the TV screen and these fluors then produce visible light. It can do that for a lot of different materials. The first thought was that there are lots of dyes that are used in fluorescence microscopy, very specific dyes that when excited by ultraviolet light give off visible light and can be then observed through a microscope. It's a very useful technique to study the chemistry of tissue and cells at microscopic levels. It would be even more useful if the resolution could be improved somewhat. So Fabian's idea was to apply cathodoluminescence--that is, visible light excited by electrons--as the signal for biological investigation, and that's what we started with.

Well, it is a very exciting instrument. It's an instrument that I liked right from the beginning, and I liked the secondary electron mode of operation as well as the cathodoluminescence. I think I liked it even more than the people at Cambridge did. The biologists that they talked to didn't see a great deal of use in it. I thought there might be a lot of use in it, and maybe that's my contribution.

Hughes: Fabian's background was not biological?

Hayes: Fabian is an electrical engineer. A very fine electrical engineer.

Hughes: What about Everhart?

Hayes: So is Everhart. The place where the SEM was developed was in the electrical engineering department in Cambridge. There is another big unit of electron microscopy at Cambridge, but that's not where this took place. The biggest application at that time and today was and is in engineering research associated with semiconductors, integrated circuits, all the Silicon Valley type of thing. They could see that that was going to be a big part of where this SEM would fit in. They looked at the biology and thought that if it hasn't got higher resolution, why is anybody going to go to this trouble to get something that isn't as good a picture? I thought in some ways the SEM produced a very useful picture and so did some of the other people here that worked on it.

Biomedical Applications

Hayes: Larry [W.] McDonald was a pathologist working here. It's an

example of the reason an interdisciplinary unit like Donner Lab is useful. The people here are here for much more than a drop-in sort of thing. Larry McDonald was here for quite a few years and he could work with us, so he brought a medical side to it. He, too, was very excited about the scanning microscope. The possibility for transferring information by this instrument was appealing to me, a kind of general look at how we learn from images. This instrument is very rich in imaging. Cathodoluminescence--the one we started with--images the chemical structure, but you could use X-rays for the elemental chemistry. You could use secondary electrons for those kind of shape pictures you see around. There is a lot of information that can be transferred. I was interested, and still am, in how we learn, in how we gain an understanding of the system through visual channels, and particularly about small systems, so that was exciting to me with respect to this microscope. Maybe what I tried to contribute was to say, "How does this work in a general way? How does the SEM fit into biological research?"

Hughes: Were you immediately applying the instrument to your research?

Hayes: Not so much to my research. That is, I didn't take it and look at lipoprotein, or I didn't take it and look at whatever things we happened to have here. But we tried to say, "Where can we now apply it so that it will answer some question in biology that is a significant, not a trivial application?" Some of the applications were just that--they were trivial. They were interesting. You could catch a fly and put it in the microscope and you could look at it, but they were not answering any of the questions that biologists cared about, outside of saying, "That's nice, and I think that that's a great picture." But you want to do more than that if it's going to have some effective utilization.

So one of the first things that we applied it to was an insect, *Tribolium*, a beetle, where the geneticists used the structure of the eye to determine the expressed genetic nature, the phenotype of the insect. So you need to know the structure of this eye. The eye is a curved surface, very hard to look at with high resolution light microscopy where the depth of focus is very narrow. You can focus up and down on it, but it's difficult. Even more difficult is the illumination and the way to look at it. It's a whole eye. You can't afford to section, even light microscopy sections. It's so difficult to put back together what the structure is. The geneticist doesn't want to know the distance between two spines accurately; he needs to know the pattern of the spines in the eye. And as soon as you start cutting, you begin to lose that pattern. Thin sections have to be reconstructed--a terribly difficult job. This [SEM] instrument is beautiful for looking at that. The geneticists would use a light microscope with large depth of focus, a dissecting scope to look at the tribolium

eye, but they were always challenged because they couldn't get enough resolution out of that system. Well, it's a very easy job for a scanning microscope.

The scanning electron microscope that they built at Berkeley was a very good microscope. It hasn't been improved upon basically to this day, except for the addition of different electron guns. The lanthanum hexaboride and the field emission guns are real steps and they do allow for considerably better, high resolution. Aside from that, the instrument that Fabian Pease and Tom Everhart built was, I think, as good an instrument as you can get today for most biological research.

Hughes: And the two guns that you mentioned were developed elsewhere?

Hayes: Yes. At that time even, Albert Crewe at Argonne National Laboratory, which is another Department of Energy lab--he is now full-time at the University of Chicago--was working on a physicists' approach to high resolution microscopy. He used almost from the beginning a field emission gun. His work I think is the place where field emission was started. Lanthanum hexaboride came as something in between the original tungsten filament and the field emission gun in performance. It's the kind of gun that we have on our instruments now. It's the kind of gun that is used in many instruments because it is a little more of a workable system than field emission for routine and for heavy use operation, and generally for most applications--certainly for ours--at low temperature. Where you are looking at bulk samples, you aren't really limited anyhow by the diameter of the probe. You are limited by other factors. So lanthenum hexaboride is a useful gun. That was developed in several laboratories; I can't really put a label on just who would have developed that.

Scanning electron microscopes really developed at Cambridge in England. The idea didn't originate there, but that was where it was developed to a point where it worked. Then it was brought to this country by those two people, Pease and Everhart, and a few others from Cambridge. It was improved some here, but the basic development was similar to the one they had built at Cambridge. Then the SEM was commercially available just a year or so later. The first was the Cambridge Instrument Company with some of the people from Cambridge University involved in that, a British company. Then just a couple of months later a Japanese company, Japan Electron Optics Laboratories. Now, they were in it from the electron optics side. They were transmission electron microscope manufacturers. And they then made the second commercial instrument.

The instrument here was immediately applied in unique ways. Everhart had a variety of applications of that instrument in

engineering and in engineering physics: studying the interaction of the electron beam in a material--what happens to it, how far does it penetrate, looking at different kinds of signals that can come out, voltage contrast; looking at ways of displaying the information. He used the deflection modulation method for the first time. So he did a lot of things with the instrument, but the instrument itself was not too much different from the one at Cambridge, I don't believe. He had already developed the Thornely Detector, still called the Everhart-Thornely Detector. It's a detector that's still used, the most common detector. He had already done that, I think, at Cambridge, so he put it out here. Here this instrument and the ones that followed were very practical, very workable, and very productive in solving some real problems in engineering and biological research.

Hughes: Were the three of you more or less choosing which projects you would become involved in? How would those decisions be made?

Hayes: Yes, I would have to rely mostly on Fabian. Tom Everhart was involved, too, but he was in a little different direction. It was Fabian who came and was interested in this biology application. And during that first cathodoluminescence study I would have to rely on him to run the instrument while I learned what the scanning microscope was about. I knew transmission microscopy for about twelve, thirteen years--something like that--but that particular scanning microscope and the setup and all had to be learned. Then after that, we'd sometimes work together. More and more as we got more projects, Fabian wanted to work on his engineering projects. He was not really a biologist. This was an interesting project that he thought he would like to do, and we did. It was published in *Nature*, and we moved on to new and generally separate experiments. So that was more and more the direction. We still would work out some shared time on the microscope. Generally in electron microscopy you spend most of the time choosing the project, first of all, and then the specimen out of that, and then preparing the specimen. By the time you sit down at the microscope, you're practically home.

Hughes: At what stage did people begin to come to you with projects?

Hayes: Pretty early. That's one thing about scanning microscope pictures--the contact is quick. A lot of people saw right away that this would be something that they would like to see, that they would like to develop. So we had quite a long list of people that would come.

Hughes: Was there any particular field that was better represented than another?

Hayes: Well, the first one I can remember was the genetics people--to

look at these parts of the insects that they use so much for insect identification. They were just a little bit below what they could see in the light microscope, and so it was just a natural for this. Besides that, the exoskeleton of insects, the fact that the skeleton is on the outside, means that they are very rugged things. You don't have to do anything really. They hold up against air drying. They will keep their own moisture and live inside the vacuum, so you can take them out and they will still be alive. The entomology work we did was from those two directions: to look at the structure in a way that would help the geneticists and a way of looking at this question of biological systems that can stand extreme changes in environment. The brine shrimp embryo is another one. They are generally called cryptobiotic material. Those were probably the first users. And then the medical people; a lot of this came through Larry McDonald, who was the pathologist. One of the early reviews of this was in the journal *Laboratory Investigation*. And we also had a lot of pathology papers.

We went to the AMA [American Medical Association] national convention in '68 with an exhibit. The AMA has a large exhibit area as part of their convention. Their yearly meetings have a very formal and established procedure for exhibits. Those exhibits also are all judged by a committee of the AMA. The exhibit won the gold medal for the year. And so then there was a lot of medical research which came in. We worked particularly with the eye with Bill [Dr. William H.] Spencer, who was the eye pathology chief at UC San Francisco. So those were the big areas. Then there were small kinds of applications: the red blood cell--trying to establish the micro-structure of blood clots.

Collaboration Outside Donner Laboratory

Hughes: It seems to me that just because of the nature of this collaborative work that you were taken outside the lab much more than any other individual in Donner Lab. Wouldn't you say that most of your collaborators were not Donner Lab people?

Hayes: That's right.

Hughes: What did that do to your feeling of being part of an institution, namely Donner Lab? Did you feel less constricted?

Hayes: No, I haven't thought of that. I always felt at home in [the] Engineering [Department] as well as at Donner. I was originally an engineer in the first part of my college training. I liked engineering and [the] Electrical Engineering [Department] is our neighbor here on the campus. We used to walk back and forth

all the time. All the fluorescence correlation for this--if you're going to do cathodoluminescence, you almost have to do the light microscopy correlation where you can say for sure what you're looking at is the dye you think you are. All of that was done here, and walking back and forth between here and Cory Hall. I feel comfortable over there [in the Electrical Engineering Department]. In fact, I still am below the line on their listing of faculty, so it is still a very good and enjoyable relationship over there. And Ted Lewis is over there, doing scanning electron microscopy and is a general bioengineer of longstanding, so that was kind of a natural connection. The San Francisco group, the things I did over there both in the urology department--we did some work on the kidney--and a very long association with the ophthalmology department.

Hughes: Did that start with them coming to you?

Hayes: Yes. At that time they'd come to us. I think the last time we went anywhere was to the AMA, because after that we couldn't keep up; we had to try and choose. Usually that would just be dependent on how large our staff was, how much we could get done, and how much the preparation and all could be done at San Francisco.

In something like '67 we got our own scanning microscope--a JEOL, one of the first of the commercial microscopes, and I guess the first commercial one anywhere devoted to biology or biomedical research--so then we were pretty much separate from the scheduling or the work in Cory [Hall]. Fabian Pease left for Bell Labs. Tom Everhart, who was shortly to become chairman, if not already chairman, of electrical engineering, so we didn't have as much contact. I had most contact through those years, as far as engineering, with Ted Lewis. After that most of the people would come to us. Most of the time what we would say is, "That's not really suitable for what we want. We have a new instrument, but it's not the best instrument for your purposes." Many times the best instrument would be the light microscope or conventional TEM [transmission electron microscope] or freeze etch--any one of the other kinds of microscopes. But sometimes you'd find one that couldn't be done other ways and we then would try to tackle that.

Hughes: So those were the criteria?

Hayes: Yes. What we wanted to do was to explore ways of learning about different systems. We had no special biological specimen that we concentrated on. We don't work on anything in particular. We are not ophthalmologists and we're not urologists and we're not geneticists, so we work on the general understanding of how we learn about the biological system through imaging. That means we would look at the questions in a different way than the person coming in with a particular sample. He wants to know something

about his particular problem. We want to know how we operate; how the process of investigation goes forth.

Hughes: Has that worked well to have these two different approaches?

Hayes: I think so. I think as soon as possible, for the most effective operation, the people who want to apply the instrument in the standard way should have their own instrument, if that's justified by the amount of use and output for that particular field. So that has occurred. There's much less now of people wanting a particular answer for a particular question, because there are lots of scanning microscopes. And I think that's good. As soon as we can, we should separate that so that there are not two purposes for the same experiment. That is better for us and that is better for them.

The Intuitive Approach

Hughes: Related to this is this idea of using more than just the object that you're investigating. You said in numerous articles that the intuitive approach is at least to be considered. Can you expound on that just a little and tell me again how scientists have responded to that idea?

Hayes: Well, it's not a new idea. It's not one I originated certainly, but it's been a part of the analysis of scientific investigation. Scientists have been interested in how they did their science. And that's been a continuing part of that. There is a considerable amount through that that has gone into the process itself. I'm looking for a book [pause] on scientific creativity. It's probably back up in the library, but it's an example of a book that looks at these type of questions. Where do ideas come from? Why do you get an idea?

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Hayes: That quote from the mathematician Poincaré is a specific comment, his distinction between logical approach and intuitive approach and what the results are. One is more of a circular process. A logical process allows you to prove to make sure that there are no errors in logic, but it may not necessarily give you the next step that you need to go on. He felt that that was a step that came from the more intuitive approach.

Hughes: How much do you think your interest in and teaching of art sped up your awareness of how this whole issue tied into electron microscopy?

Hayes: I wouldn't say I taught art, but I was teaching science in an art school. Art was the central subject. That's true. That was a good experience, and I think it did change how I approached this later on. I think very often the younger person has more total confidence in the logical process, in the analytic approach. So while I enjoyed the art school experience very much, I think I was not turned in that direction very much at that time because I was quite young. I think it was bound to be remembered, though, and to be a part of what came about later.

One thing it did show me was that there are some areas that are very difficult to teach. In the teaching of science, for example, there is considerable advantage to the fact that much of the content of the course can be put down as symbolic representation of ideas. You can write, or you can put on the blackboard, or you can lecture and say what the content is. You may not be able to inspire or you may not have the fine touch of selection and emphasis and all of those sort of things, but the basic material is there. Whereas when you come to teach art, you can't even tell yourself what you're trying to get across. You can be there essentially as a critic to say, "No, I don't think that's good," or, "Yes, I think that's fine," or, "That's exciting, what you've done." But it's a much slower, less well-defined process. And I think that stayed with me. It impressed me that all of my education has been a kind of technical education, even in courses like history. There is a kind of technical education approach to history that is not in the fine arts. I had very little in fine arts. So that I think was a part of a period that was useful because it made it more likely to occur that I might look at some of the areas in science that are difficult to understand and say that maybe that's like the arts, that you cannot put it in such a rigid structure.

Hughes: Is that essentially why the older man perhaps is more open to these things? It's a matter of experience and learning that there are areas that are more difficult to transmit?

Hayes: Yes, I think so. We don't teach very many failures; we teach successes. And as you go along, you find that most experiments don't work. You find that most times when you want to persuade someone of an important philosophical point, you fail. Most of the time when you want to inspire extra work from the people around you on the basis of your own interests, you fail.

It's a very trite saying, and I'm not enough of an artist to know at all whether it's true, but there is a feeling in art that you have to suffer to be good. I think there is a component of going along through life that is missing in the young person. That generally the young person, particularly in our country, and particularly when I was growing up, there was very little

suffering in my life. Just the opposite. It was a very encouraging, a very optimistic environment. No matter what the environment of support is, no matter what you do, there is a certain probability of suffering, of hurt, that comes in. And those come about at random times. As you grow older it's just that there has been more time for this to occur. And I think generally, then, as people get older they find that not all solutions are under their control. As you do that, you tend to say, "If I can't control it, if I can't psyche it out, if I can't use my logical processes, then what do I do?" So you explore a little more other areas. If all the questions could be answered in logic, I would probably be more heavily into logic as the primary route for discovery.

Heavy Ion Radiography

Hughes: I know you've been working fairly recently on the heavy charged particle microscopy. With Dr. Tobias?

Hayes: Yes, he is really the heavy particle person.

Hughes: Is that exciting to you in the way that the scanning electron microscope was to you in the early sixties? Is it a similar kind of breakthrough?

Hayes: To me personally, it doesn't represent nearly as broad an application. The scanning microscope is like a candy store: you can have information on so many modes, so many ways that you can apply this, so many different kinds of signals that come out of the specimen. What I would say is that the heavy ion radiography is like one mode. It's as if we were going to say, "We have another addition to this battery of techniques that you could utilize to image characteristics of the system. And that's partly because I'm only involved in this particular heavy ion microradiography study, not even heavy ion radiography generally, and not certainly heavy ion at all.

I'm interested in the kind of information that you can display in an image with the heavy ion technique, partly because of the unique interactions between heavy ions and parts of the system. What is it that stops the heavy ion? How does it interact? You can learn some unique things there. And also because of the way that we record the image. That is interesting to me. In heavy ion microradiography, instead of recording shades of gray or shades of color, or shading anyhow, what you do is make a plate where the differences in the signal are recorded as differences in height in the plate. And then you image that height difference. It

might be an electrical property that is represented as height, or it might be a density property but it is represented as height, so you build up in space a structure that corresponds to the signal that you're trying to read off. What most interests me about this is how do we interact with information when it is built up like that. You've probably seen computer print-outs that represent, say, three variables as a graph in space. It prints out these peaks and mountains, and as you look at that you say, "Oh, yes, I see that this peak is in the x,y plane and it has a certain height, too." Well, those kinds of things are constructions to allow us to interact with the graph. And in a sense, the heavy ion radiograph is a graph, a kind of unique graph. I don't see it as broad as what we were interested in early SEM when ten modes opened up at once.

Fly Ash

Hayes: Want to talk about fly ash? [laughter] I'm interested in fly ash, too.

Hughes: What about fly ash?

Hayes: Well, I'm interested there, not so much that it's the fly ash particularly, although that's an important component of environmental pollution, but in this question of localization in space. Again it's a kind of spatial analysis. Is it important that the elements of fly ash differ from one particle to the next? The particles are only a micron in size. Is it important that the one is different from the next? And that does interest me because it reflects a kind of interaction between the organism and its environment that is kind of special and sometimes I think has been overlooked.

The unit that is going to interact in the biological system almost always is the cell, a very small unit. We don't really interact with lungs. We say it's going to hurt our lungs, but what it's really going to hurt are the cells. The cell is the unit that responds to the pollution with a genetic aberration, with a mutation or in a carcinogenic transformation. The cell is the thing that changes. And so we should look at the kinds of comparative-sized units that will interact at the cell level. If we say it is the whole lung and look at the whole average chemistry of all of the particles, we won't be able to tell what is the exposure of that sensitive unit, the cell. Unless we do understand this kind of distribution among individual particles, we don't know what the individual cell does. How does the individual cell respond to its own environment? So there it's a

kind of microanalysis. But instead of looking at extremely low concentrations of material in a bulk sample, we are micro in the sense that we look at fairly high concentrations of, say, titanium or cadmium or zinc--but in a very small package in space. That's the micro part of our micro. So what we're interested in there is to see if there is a part of exposure to our environmental hazards that has to do with the packaging of those hazards into very small spatial units--units that are approximately the same size as the cell. That's the end of fly ash comments.

The Biophysics Student

Hughes: Do you have anything to say about what you see as the future of Donner Lab? The directions that might be taken? Including your own work?

Hayes: Well, it's a very hot area. The students I think are very, very vital to the operation, the whole progress of the laboratory. You could go back all the way to the beginning of the laboratory and see that the students were always very important. They are just as much today, and they're just as enthusiastic and hard-working.

Hughes: What is it that excites them particularly?

Hayes: I don't know. I've thought about that some. Some of it, I think you have to say is an appeal to the student who can feel very comfortable with a theoretical idea, in a quantitative environment. First of all, he's always done well in math and chemistry. He's always good in any kind of physics or engineering, so he's attracted technically to the field, but he also likes to work with the living system. [pause] He likes the kind of warmth that goes with biological investigation and also is very good technically. So they come in as very good students in math and physics, but they don't want to be physics majors and so they come to biophysics as something that gives them a chance to do both. It brings them into a biological area and still requires the kind of quantitative approach that they are comfortable with and good at.

Some of it too has to do with practical things. They see biophysics as a good preparation for medical school or for some of the other biological areas that they may have perceived as more open than some of the physical science areas. So I think that's why they come. They're very enthusiastic, I must say. They are just great.

Hughes: Well, Dr. Hayes, it's getting late. Do you want to stop?

Hayes: Yes.

Transcriber unknown

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TAPE GUIDE--Thomas Hayes

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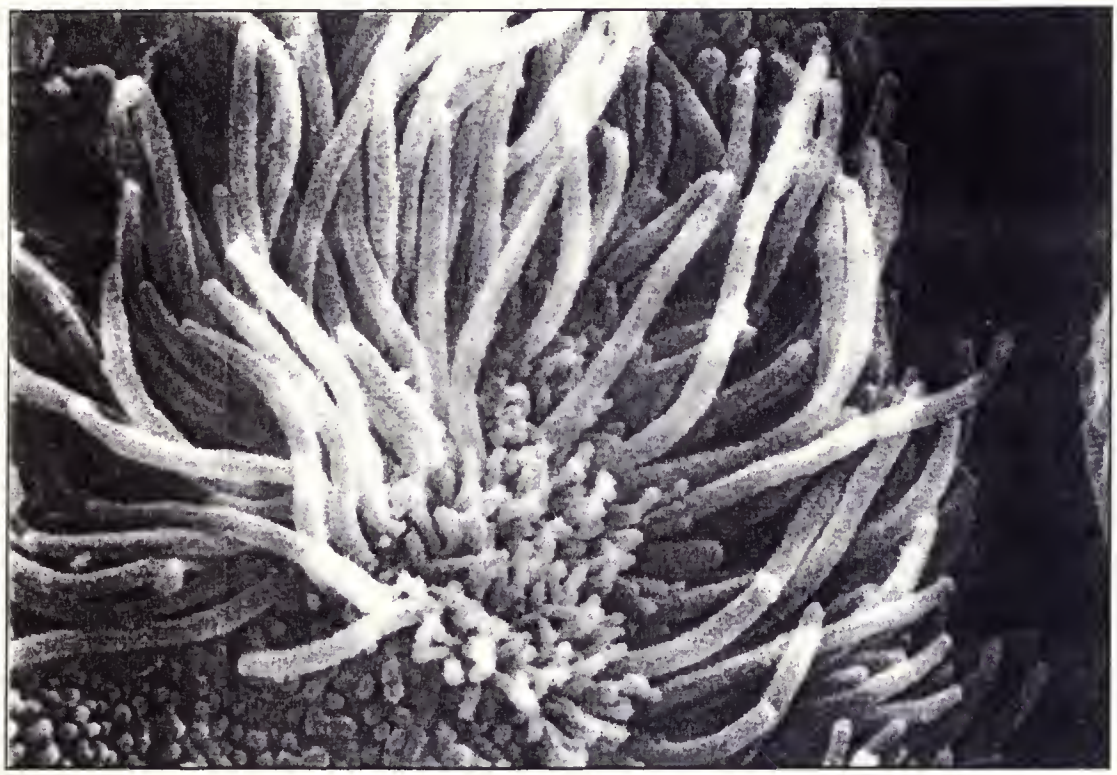

Scanning electron micrograph of single cell from the airway surface in a mouse lung. Magnification is 17,000 times. Micrograph taken by T. Hayes and S.J. Bastacky on January 11, 1977.

ART AND SCIENCE IN IMAGING

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To the artist, the subjective interaction with his environment is the accepted and traditional mode of information transfer, but to the scientist, this kind of subjective contact often can seem less familiar and less productive. Aharon Katchalsky, however, was perfectly comfortable using both the tools of the artist and the tools of the scientist. Poincaré has stated, "it is by logic that we prove but by intuition that we discover," and if we are to be about the business of discovery, it is necessary to open ourselves to the intuitive, subjective approaches to the specimen. I believe Aharon Katchalsky stimulated his listener to bring his entire self to the process of discovery.

The artistic approaches are particularly applicable when using microscopes that present the opportunity for the observer to make visual contact using the same modes of information transfer that are available to him in the large world around him. An instrument such as the scanning electron microscope provides both analytic information in the form of geometric, chemical, and physical analyses and also opens up the possibility for intuitive, experiential contact. The results of this contact, while not as neat or predictable as with the objective analytic approach, are valuable additions to our methodology of knowing.

Our perception of an object may fall into one of three categories as suggested by Arnheim in his book, "Visual Thinking" (R. Arnheim, Univ. of California Press, Berkeley, California, 1969):

(1) The observer may not take any pains whatever to separate the context from the object and may perceive the entire system as a camera might record it. Such an attitude of perception might be described as "realistic."

(2) The second type of perception attempts to peel off context and to extract the essence of the object. Such perception is generally identified with scientific investigation and is what might be called "practical" vision.

(3) The third type of perception sees context as separate from the object but does not try to get rid of context, but rather welcomes contextual changes as a means of revealing the deeper nature of the object. This third perceptual

mode is more commonly associated with the artist than the scientist and in painting, the school of Impressionism is a good example of this type of perception. The Impressionist welcomes changes in context. The changing aspects of the cathedral at Rheims as revealed to the artist in the morning, at midday, and in late afternoon provide a somewhat different insight at each time into the nature of this structure. The interaction between the object and its context over a range of contextual situations reveals properties of the object that would not be apparent from any single context.

FIG. 1. Visual contact with a leaf surface (Pelargonium) allows us to explore the microworld with intuitive tools.

The first type of perception mentioned above ignores the effect of context on the subject; the second type eliminates context in favor of a uniform and perhaps overly rigid "idea" of the object; the third type of perception utilizes the interaction between an object and its surroundings in an attempt to understand the nature of the object itself. The changes in context become a method for probing the nature of the object. Again quoting from Arnheim, the artist "proceeded from impressions of the whole; from a connection of things." Such a holistic approach on the microscopic scale permits the observer to investigate relationships between the parts rather than exhausting himself in an increasingly unrewarding study of individual units. The world seen through the microscope is a small one, but the methods of approach need not be restricted to an equally tiny base.

At times it would seem that it is necessary to transform the image, at least in our perception, so that realism is lost in order that some deeper significance can be recognized. Picasso has said, "painting is poetry and is always written in verse with plastic rhymes never in prose." Perhaps we could apply some of the methodology of the arts in a fundamental way to the study of our imaging problems in science. Picasso's figures are not faithful to metric or projective geometry. However, if we dismiss such an image on the basis of its lack of fidelity to measured distance or angle, we will miss an opportunity to gain a better understanding of the object represented—in this case the human figure. Similarly, if we limit our perceptions to a reduction of objects to their stereotyped idea symbols, we may miss an opportunity to extend our understanding of the objects represented in our micrographs. The Impressionsist school of painting has been described as an example of "abandoned constancy." In somewhat more scientific terms we could describe the same process of abandoned consistancy as invariance under a variety of transformations. Our traditional premise that we should try to maintain all of the characteristics of the specimen without change forms a wall to protect us against unrecognized artifacts in specimen preparation, aberrant objects in our microscopes, misleading display and processing steps, and overemotional response by the observer. However, walls erected for protection have a tendency to become prisons—perhaps we can explore the usefulness of an occasional sortie outside of these walls. Within science we might well experiment with the subjective approach of the artist in order to give us the personal contact so necessary for intuitive discovery.

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